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VALIDATION OF IMPEDANCE CARDIOGRAPHY AND ITS USE IN THE EVALUATION OF EXERCISE RESPONSE AFTER MYOCARDIAL INFARCTION

BY

DOROTHY MAXINE HETHERINGTON

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M. Hetherington

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Permanent Address:

12304 - 28 Avenue
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Date: October 2, 1986

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled VALIDATION OF IMPEDANCE CARDIOGRAPHY AND ITS USE IN THE EVALUATION OF EXERCISE RESPONSE AFTER MYOCARDIAL INFARCTION submitted by Dorothy Maxine Hetherington in partial fulfilment of the requirements for the degree of Master of Science in Experimental Medicine.

Supervisor

Richard E Rossall

Date: October 2, 1986

DEDICATION

To Ross, Shawn, Clarke and Lia

ABSTRACT

It is generally accepted that measurements of ventricular function obtained at rest are poor predictors of the cardiovascular response to exercise. Impedance cardiography is a non-invasive method that can measure stroke volume and cardiac output during exercise. This series of investigations were undertaken to determine the accuracy and reproducibility of the cardiac output measurements made by Impedance Cardiography and the stroke volume-heart rate relationship in endurance trained athletes and in patients with coronary artery disease.

No systematic error was demonstrated between impedance cardiography and the direct Fick Method over the range of 3.5 to 18 l/min made in 20 patients. The random error of the cardiac output and the stroke volume measurements at rest and during exercise was found to be <5%. The reproducibility during maximum exercise response was assessed in 6 young athletes who underwent 2 maximum exercise tests, one week apart, on a bicycle ergometer. Highly significant correlations were obtained in the stroke volume (r=0.84, p<0.001) and cardiac output (r=0.98, p<0.001) between the two tests. Reproducibility for cardiac output and stroke volume in patients with left ventricular dysfunction over one week was highly significant (r=0.94, p<0.001; r=0.93, p<0.001) respectively.

Impedance Cardiography was incorporated into routine exercise testing on a bicycle ergometer in 15 patients with left ventricular dysfunction. In 8 patients, the stroke volume response to increasing heart rates was abnormal. Cardiac output was attenuated throughout exercise in this group while heart rate was increased.

Thirty-nine, non-beta-blocked, asymptomatic patients were studied 8-10 week following an acute infarction. Nine normal age-matched sedentary adult males were studied for comparison. The patients were separated into three groups based on the stroke volume-heart rate relationship during graded upright exercise. Group A (n=14) exhibited a normal stroke volume-heart rate profile. Group B (n=13) increased stroke volume initially then decreased stroke volume ≥15% at heart rate >100-105 beat/min. Group C (n=12) failed to increase stroke volume during exercise. Group A exhibited a response to exercise that was similar to the control group. Group B had an enhanced mean arterial pressure and vascular resistance at rest and throughout exercise while heart rate increased in a similar fashion to Group A until work of >70W was undertaken at which time heart rate increased in a curvilinear fashion and cardiac output was attenuated. Group C exhibited an attenuated cardiac output, a higher heart rate and failed to decreased vascular resistance normally during exercise.

Results from these investigation indicate that:

1. Impedance cardiography is a non-invasive technique which is as accurate as the Direct Fick Method. Short and long term reproducibility was comparable to invasive techniques.

2. The stroke volume-heart rate profile in post MI patients delineates a subset of patients who respond to exercise abnormally (a reduced ventricular function and an increased vascular resistance). These patients can be identified by Impedance Cardiography during a routine stress test.

3. Identification of this group of patients may be important in determining prognosis and planning long term therapy.

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CHAPTER I

BACKGROUND INFORMATION

INTRODUCTION

Myocardial infarction is a major health problem affecting the population below the age of 65 years. About 500,000 patients are hospitalized annually in the United States with an acute infarction (1). Canadian statistics (1980-81) indicate that ischemic heart disease was ranked second as the cause for the most days of hospital care needed (2). In addition, ischemic heart disease is the leading cause of death in both Canada (2) and the United States (2,3) with most of these deaths occurring suddenly prior to hospitalization (3). Among persons who have suffered an infarction and leave hospital, the number of patients suffering a second event (death, second infarction, unstable angina) approaches 50% in the first year following the acute episode (4). In addition, a 3- to 4-fold increase in the risk of death persists even 10 years following the initial event (5). It has been reported recently that 65% of patients who develop congestive heart failure, which carries with it a low 2-year survival rate, have significant coronary artery disease (6). The magnitude of these statistics suggest that effective means of evaluating cardiac function are required, especially inexpensive ones which could be used in the outpatient setting.

Assessment of the functional capacity of the cardiovascular system is best done during the stress of exercise (7,8). The capacity of the cardiovascular system to respond to the increased metabolic demands that occur during exercise is achieved by alterations in heart rate, stroke volume (hence cardiac output), peripheral resistance and venous capacitance (9,10). These cardiovascular adjustments to exercise are coordinated by the central nervous system. Information is relayed from the periphery to the central nervous system and integrated into an effective output from the nervous system to the cardiovascular system (11).

In the normal individual, free of heart disease, the cardiovascular system changes in a predictable fashion in response to graded dynamic exercise. Heart rate and stroke volume both increase to produce a 5 to 8-fold increase in cardiac output during maximal exercise. The heart rate increases 2-3 fold while the stroke volume usually doubles (12,13,14). When a normal subject exercises in the upright position, the stroke volume increases until the heart rate reaches 110-120 beat/min. Thereafter the heart rate alone continues to rise until a near maximal workload and heart rate is reached (13). The stroke volume remains at a maximum value by the utilization of the diastolic and systolic reserve mechanisms (14,15). In some patients with ischemic heart disease, the inotropic response to sympathetic stimulation may be blunted and the stroke volume is increased by the Starling mechanism alone (15). When the Starling mechanism is utilized fully in these patients, stroke volume becomes extremely sensitive to alterations in afterload and the stroke volume will decrease (16). The ability to identify patients with a limited diastolic and systolic reserve during exercise may be important in predicting prognosis and in planning long term therapy.

Left ventricular function is generally assessed by evaluating the determinants of stroke volume (i.e. end-diastolic volume or pressure, end-systolic volume or pressure), cardiac output and/or by evaluating contractility (ejection fraction, velocity of circumferential shortening) and ventricular wall motion. Current techniques available for evaluating these parameters include formal cardiac catheterization, insertion of flow directed catheters, radionuclide ventriculography and echocardiography. Being invasive, the first two methods are not without risk to the patient and cannot be performed repeatedly on all patients suspected of having heart disease. In addition, these procedures require expensive equipment and experienced, well trained personnel. With the development of echocardiography and radionuclide ventriculography, it has been possible to obtain a great deal of information regarding ventricular function non-invasively. However, these methods also are costly and require well trained personnel for acquiring and intrepreting the data. Further, radionuclide studies use radioisotopes and again are not readily repeatable. All these methods are usually performed in the recumbent or semi-recumbent position and are difficult to perform during exercise.

The long term management of the cardiac patient requires assessment of ventricular performance periodically over months or years. This requires a procedure that is acceptable to the patient (that is non-invasive), highly reproducible and inexpensive. Due to the limitations of the conventional techniques for evaluating myocardial performance, it is proposed that impedance cardiography may be a method with possible application for use in the cardiac patient. The method compares favorably with standard techniques for measuring cardiac output (see review 17). Using this technique it has been possible to monitor the expected biological variation during exercise or postural changes (18,19).

It is suggested that impedance cardiography could be used to document the stroke volume-heart rate response in both normal subjects and cardiac patients. Although the stroke volume and heart rate change in a predictable pattern during graded upright exercise in the normal subjects (12,13), the corresponding pattern is not known with certainty in patients with left ventricular dysfunction and in patients following an acute infarction. Further, evaluation of this relationship in patients with known cardiac disease may be important in defining left ventricular function.

Hypotheses to be Tested

1. Measurement of cardiac output using Impedance Cardiography correlates positively and significantly with cardiac output measurements using the direct Fick method.

2. The random error or short term repeatability of the cardiac output and stroke volume measurements using the Impedance Cardiography is acceptable for clinical use.

3. Measurement of cardiac output carried out one week apart in healthy endurance trained athletes is reproducible.

4. Stroke volume-heart rate profiles can be generated non-invasively in submaximal and maximal exercise in well trained athletes.

5. Measurement of cardiac output and stroke volume carried out one week apart in patients with heart disease is reproducible.

6. Stroke volume-heart rate profiles can be generated non-invasively in patients with left ventricular dysfunction.

7. Stroke volume-heart rate profiles can be generated in patients at 8-10 weeks following an acute myocardial infarction by impedance cardiography.

DETERMINANTS OF CARDIAC PUMP PERFORMANCE

Evaluation of myocardial performance is usually focused on the ability of the left ventricle to act as a pump. In a given situation, the determinants of cardiac output are the heart rate and stroke volume. Although heart rate and stroke volume are often approached as being independent factors in the control of cardiac output, these two variables are interdependent (14). The factors that affect stroke volume will be discussed in the following section and include: the preload, afterload and contractility of the ventricle.

Preload

Principles of myocardial performance, based on the existing knowledge of the skeletal muscle length-tension relationship was investigated by Starling and co-workers, and published in a series of classical papers between 1912-1920 (20,21,22). This series of investigations demonstrated the fundamental relationship between fiber length and cardiac performance. Starling's law of the heart was subsequently formulated and states that "the energy of contraction is a function of the length of the muscle fiber" (22). This law is an expression of the length-tension relationship and defines ventricular function as a function of variations in preload. In the intact heart, increases in preload or the end-diastolic volume result in an augmentation of the extent and velocity of wall shortening and therefore an increase in stroke volume (20).

The concept of diastolic fiber length as a principle physiological determinant of systolic function was rejected initially. However, in

1954 Sarnoff and Bergland showed experimentally that the relationship between diastolic fiber length and systolic performance (stroke volume or stroke work) is characterized by a family of Starling curves (23). The stroke work was shown to change in relation to left atrial pressure under different experimental conditions (i.e. sympathetic stimulation or a change in afterload) without changing the basic shape of the ventricular function curve. These investigations formed the basis for the ventricular function curves in the intact, ejecting ventricle, which relates ventricular end-diastolic volume or pressure to stroke volume and stroke work (23).

Mechanisms whereby changes in the initial length altered tension development in striated muscle was defined by studies which correlated muscle ultrastructure with function (24). The relation between sarcomere length and isometric tension development was determined initially in skeletal muscle by Huxley and co-workers (25,26,27). Later Sonnenblick et al (1963) found that force development in cardiac muscle was greatest at a mean sarcomere length of 2.2u with force decreasing sharply at both shorter and longer lengths (28). These investigators explained both the ascending and descending limb of the Starling curve by this mechanism (28). A review of the subject was presented later by Sonnenblick in 1974 (29). Recent evidence suggests that the increase in developed tension which occurs from increasing fiber length is partially linked to a length-dependent calcium release mechanism resulting in a greater number of troponin-C units bound by calcium ions (30).

The intact heart appears to behave differently from isolated tissue as it appears to resist overstretching (15,31). This may in part be explained by a change in the orientation of the different muscle fibers when distention occurs. When the ventricle is distended, filling pressure rises markedly with small increments in ventricular volume. Small increases in sarcomere length accompany these large increases in ventricular pressure (32).

It is generally accepted that in the erect posture, the normal ventricle operates on the ascending portion of its function curve where there is almost a linear relationship between the amount of energy produced by the contracting ventricle and the pressure or volume of the ventricle at end diastole (31,33-35). A limitation of the Starling mechanism has been demonstrated in dogs during ventricular ischemia, both following an increase in afterload, and on assuming the supine posture (36). It appears that under these conditions, the ventricle functions on the steep portion of the ventricular pressure-volume curve where slight increases in volume are accompanied by marked rises in left ventricular end-diastolic pressure.

Although some investigations indicate a limitation of the Starling mechanism in the normal ventricle, its usefulness has been reaffirmed repeatedly in the clinical setting in patients who exhibit left ventricular dysfunction, myocardial infarction and when filling pressure is reduced. In these situations it is possible to increase stroke volume, stroke work and cardiac output using a volume challenge and/or an afterload reducing agent (33).

There remains controversy concerning the existence of a descending limb of the cardiac function curve in the intact left ventricle. Evidence indicates that elongation of the sacromere and disengagement of the actin and myosin myofilaments does not occur at high end-diastolic volumes (31,32). In addition, no descending limb in the developed wall stress or systolic pressure is evident until the ventricular end-diastolic pressure exceeds 60 mmHg. At this time ventricular pressure declines 7.5% at an end-diastolic pressure of 100 mmHg (32). However, a descending limb of ventricular function is apparent the when diastolic pressure exceeds 30 mmHg following an initial increase in aortic pressure (16). When aortic pressure is increased during volume loading, an increase in wall stress accompanies the decrease in stroke volume (16,37). This descending limb of ventricular function (i.e. a fall in stroke volume) may result from reduced fiber shortening due to an increased afterload at a time when the sarcomere length and preload of the ventricle is maximal and not due to a depression of cardiac performance (i.e. a decrease in systolic pressure or wall stress) (16,37).

The major determinants of ventricular filling and therefore end-diastolic volume and fiber length which are of relevance in ischemic heart disease and exercise are: (i) ventricular relaxation, (ii) right ventricular pump function, (iii) the non-contractile portion of the properties of the left ventricle e.g. scar tissue, (iv) body position, and (iii) capacitance of the venous system. The first two topics will be discussed in more detail.

Ventricular Relaxation

Except for the controversial concept of ventricular suction (38,39), the importance of ventricular relaxation to ventricular function was largely ignored and was considered to be of less importance than the systolic function. Myocardial relaxation is an energy dependent process that consumes high energy phosphates (40,41). Calcium is released from the troponin and sequestered into the sarcoplasmic reticulum and across the cell membrane during this period. Relaxation in the isolated cardiac muscle not only appears to be a function of an energy dependent component but also appears to be related to muscle length and load (41). There is little agreement as to the hemodynamic determinants of relaxation in the intact left ventricle. Some investigators reported an inverse relationship between the rate of relaxation and systolic pressure or length (42-44). A more complete review of the topic is given by Brutsaert et al in 1980 (45).

In various forms of heart disease, relaxation can be affected before systolic abnormalities are apparent. Angina pectoris is associated with an apparent stiffening of the left ventricular chamber which is thought to be caused by impaired or slowed myocardial relaxation (46,47). Evidence of impairment of relaxation during ischemia includes a lower maximum rate of pressure decline, prolongation of isovolumic relaxation and an increase in the time constant of isovolumic pressure decline (46,48). In addition to this impairment of diastolic function, there is also evidence of impaired contractility (47). Whether this abnormal ventricular function represents an inability of the sarcoplasmic reticulum to take up calcium or whether it is due to an alteration in the load dependent aspects of ventricular systolic function is not known.

In the normal ventricle, the rate of pressure decay increases significantly and filling pressures remain unchanged or increase slightly during exercise (48). On the other hand, in the ischemic ventricle, the rate of pressure decay is reduced and filling pressures are abnormally elevated during exercise (48). Ischemic hearts exhibit an augmentation of the early filling apparently because of an elevated left atrial pressure (49). A reduction of late diastolic filling is also observed due possibly to an increase in the ventricular impedance as a result of a slow and asynchronous wall motion during relaxation. These factors may account for the frequently observed elevation of left ventricular end-diastolic pressure resulting in the higher resistance to filling associated with acute myocardial ischemia (49-51).

Right Ventricular Function

Until the early 1970's, right ventricular function was generally felt to be unimportant to the function of the left ventricle. Weber et al (1980) reviewed the interrelationship of the normal right and left ventricle (52). Mechanical events that occur in one ventricle under normal physiological conditions affect the other. Cohn et al reported the findings in 6 patients with acute myocardial infarction who had predominant involvement of the right ventricle and who presented with cardiogenic shock (53). Subsequent studies have corroborated their findings of elevated right ventricular pressures and low cardiac output in patients with infarction of the inferior wall of the left ventricle and with right ventricular involvement (54).

Further, animal studies demonstrated that after extensive cauterization of the lateral wall of the right ventricle, there was a 20% reduction of cardiac output (55). Volume loading in this preparation resulted in a marked elevation of right heart filling pressures and improvement in cardiac output (56). When the pericardium was intact, the typical hemodynamic pattern was produced (56). Subsequent pericardiotomy resulted in a significant increase in cardiac output and mean arterial pressure. These results suggest that the pericardium limits left ventricular filling when the right ventricle is acutely dilated. In this situation, filling of the left ventricle is impeded by a reversal of the transseptal pressure gradient and a leftward septal shift (55).

Afterload

Afterload is defined as the tension, force or stress which is encountered when the muscle attempts to shorten. Afterload describes the external factors that oppose fiber shortening and ventricular ejection (57). In isolated papillary muscle studies, the importance of changes in afterload on myocardial contraction was demonstrated by Sonnenblick and co-workers (57). The afterload was taken to be the load in addition to the preload that the muscle must counteract during shortening. The lower the afterload placed on the isolated muscle, the greater the velocity and extent of shortening during contraction. An increase in the afterload resulted in a decline in the velocity of shortening and in the extent of shortening (24,58).

Problems arise when attempting to extrapolate the information from the isolated cardiac muscle to the intact ventricle. Attempts have been made to use instantaneous ventricular wall stress as a measure of afterload. This requires knowledge of the instantaneous chamber dimension, chamber pressure and changes in these parameters during ejection (see review 60). Since accurate and reproducible measurements of aortic pressure are simple to obtain, this parameter has also been used extensively as a measure of left ventricular afterload (60). In addition, left ventricular pressure has been used as a measure of afterload (60) either averaged over the entire cardiac cycle or over the ejection period and related to cardiac output or stroke volume (61). All these methods have been criticized as being inadequate in defining afterload in the intact ventricle since knowledge concerning the properties of the arterial system are not accounted for (60). Afterload in the intact ventricle is determined by: (i) the compliance of the large vessels, (ii) the tone of the resistance vessels, (iii) the viscosity of the blood and (iv) the reflection of the pressure and the flow waves from the periphery (60).

Recently, investigators have suggested that aortic input impedance characterizes total afterload more accurately (60). Impedance defines the opposition to arterial blood flow including both the nonpulsatile (peripheral resistance) and pulsatile components (aortic compliance and wave reflections).

The peripheral vascular resistance or the ratio of the pressure drop across the cardiovascular system and the flow through the system is often considered to represent ventricular afterload in clinical studies. In the systemic circulation, the peripheral vascular resistance is linearly related to blood viscosity and inversely related to the fourth power of the radius (60) with the caliber of the arteriolar bed exterting the most influence on the resistance to ventricular ejection. Arteriolar vasoconstriction and vasodilitation are controlled by neural, humoral or by metabolic factors (11). Although total peripheral resistance is commonly calculated in clinical studies, this measurement does not take into account the elastic properties of the system and wave reflections and is not as adequate in describing afterload as the aortic input impedance (60). However, this latter technique requires sophisticated equipment (60).

Afterload is a key determinant of the extent of muscle shortening and the quantity of blood ejected by the intact ventricle. The performance of cardiac muscle for any given state of contractility depends on its length prior to contraction (preload) and its loading conditions during contraction (afterload). At any one muscle length and state of contractility, the maximum shortening and velocity of shortening are inversely related to the afterload (62,63) (see Diagram 1). When the sarcomere length is optimal and the preload is maximal, an increase in the afterload results in a decrease in stroke volume (16). In addition, when the inotropic state of the heart is depressed, an increase in afterload will have a detrimental effect on myocardial shortening. Hence, when left ventricular function is impaired (i.e. decreased contractility and maximum perload), afterload becomes an increasingly important determinant of cardiac performance (16,37).

Diagram 1

The material on this page has been removed because of the unavailability of copyright permission. Diagram 1 illustrates the effects of changing: (i) perload when afterload and contractility are held constant, (ii) afterload when preload and contractility are held constant, and (iii) the inotropic state when preload and afterload are held constant. Wall shortening, tension, left ventricular pressure, aortic flow and the end-diastolic pressure are illustrated under these different conditions during an isotonic contraction, isovolumetric contraction and a normally ejecting contraction. Source of the diagram:
Braunwald E, Ross J, Sonnenblick EH. Mechanisms of Contraction of the Normal and Failing Heart. Boston: Little,
Brown, 1976: page 112.

Contractility

In addition to the two fundamental properties of cardiac muscle which determine the velocity and extent of fiber shortening (i.e.preload and afterload), a third factor, contractility, also determines fiber shortening. It reflects the "strength" of contraction of the myocardial fibers and is influenced by neurohumoral stimuli and by the metabolic state of the myocardium (15,31).

Sarnoff et al (23) first introduced the interrelation between Starling's law and the concept of myocardial contractility. Contractility was augmented by infusing catecholamines. Results indicated a shift of the maximum force-length relationship upward and to the left. The myocardium generated more force at any given volume or fiber length when contractility increased (23,64,65). Positive inotropic agents augment the force-velocity relationship by increasing the work done at any one afterload (64). Therefore, an increase in the contractile state of the myocardium can increase the stroke volume, ejection fraction and ejection rate if the fiber length and afterload are maintained (see Diagram 1). Alternatively, negative inotropic agents (i.e. propranolol, hypoxia or ischemia) depress the myocardium and shift the force-length curve downward and to the right (23) and shift the force-velocity curve downward and to the left (66). A decrease in the contractile state will result in a decrease in stroke volume, ejection fraction and ejection rate at a constant fiber length and afterload (15).

In 1959 Abbott and Mommaerts published the first characterization of the mechanical behavior of the cardiac muscle that used the force-velocity relationship for data analysis (67). Positive inotropic changes induced by the staircase phenomenon and post-extrasystolic potentiation were examined. During the next 25 years, research has focused on the mechanism of myocardial contraction and the regulation of myocardial contractility.

Knowledge of the role of the calcium ion in the regulation of myocardial contraction has been recognized from a series of observations starting in 1883 when Ringer found that calcium was essential for cardiac contraction (68) and later confirmed in 1947 when calcium was injected into a single muscle cell resulting in contraction (69). In the 1960's, the mechanism by which calcium regulates muscle contraction and relaxation was clarified further. Membrane vesicles in the sarcoplasmic reticulum were found to transport calcium into their interior and also had the ability to add calcium ions into the cell (70). The role of calcium ions in regulating myocardial contractility stemmed from the work of Weber and Winicur who clarified the effects of calcium on skeletal muscle actomyosin by defining the role of calcium in activating Mg-ATPase activity (71).

The force developed by the myocardium is regulated by the cytoplasmic calcium concentration and the number of troponin-C units bound by calcium which in turn determines the interaction of the actin and myosin myofilaments (72). Relaxation subsequently occurs when calcium becomes dissociated from troponin-C as calcium is sequestered back into the sarcoplasmic reticulum and across the cell membrane. Major sources of calcium available for troponin-C binding include calcium contained in the extracellular fluid, bound to the cell membrane, in the sacroplasmic reticulum, mitochondria and in the cytoplasmic ionic pools bound to intracellular buffers and proteins. The source of calcium used to initiate contraction is controversial. Present evidence suggests that calcium enters the cell through voltage activated gated slow channels during the plateau phase of the action potential. The initial rise in intracellular calcium causes a secondary release of calcium from sites within the cell (i.e. sarcoplasmic reticulum) thus increasing the calcium concentration in the cytoplasm. Calcium binds to the troponin-C complex causing a conformation change which allows the myosin to interact with the actin myofilament, utilizing ATP as an energy source for muscle contraction. Beta-adrenergic agonists appear to affect the calcium entry into the cell, the release of calcium from sites within the cell and the calcium uptake by the sacroplasmic reticulum (72,73).

The functional effects of positive inotropes (i.e. beta-adrenergic agonists) are an enhancement of myocardial contracility with a subsequent shortening of systole, an increased velocity of contraction and an increased rate of relaxation. The mechanism for these actions of the beta-adrenergic agonists was elucidated by the discovery of the role of cyclic adenosine monophosphate (cAMP) as an intracellular messenger (73,74). Through the action of cAMP, beta-adrengeric agonists increase the slow inward current by an increase in the number of calcium channels opened. This results in an increase in calcium ion influx into the cell across the sarcolemma and an increase in the amount of calcium released from the sarcoplasmic reticulum vesicles and other intracellular stores. The increased release is also accompanied by an increased uptake of calcium by the sarcoplasmic reticulum vesicles (72). Both effects (i.e.

increased rate of calcium uptake and release by the sarcoplasmic reticulum) are believed to be mediated by the phosphorylation of phospholamban, a membrane protein (72).

Contractility appears to be depressed in many forms of heart disease including heart failure and ventricular dysfunction (73). The mechanism for this depression is unknown. Cardiologists and cardiovascular physiologists use a number of parameters in an attempt to evaluate contractility in the clinical setting. At present, there is a tendency to use the left ventricular ejection fraction as a measure of the overall myocardial contractility despite the effect of heart rate, preload and peripheral resistance on the ratio between stroke volume and end-diastolic volume (73,75). Measurements of cardiac performance obtained during the isovolumic phase of contraction (i.e. dp/dt) or during the ejection phase (ejection fraction, systolic ejection rate and velocity of circumferential fiber shortening) are other methods of assessing contractility. However, many of these indices are not independent of loading conditions.

End-systolic volume at a given end-systolic pressure is, however, independent of load and has been shown to vary with contractile state (63,76). The end-systolic pressure-volume relationship can be used to evaluate clinically the contractile state of the myocardium (76). These pressure-volume relationships can be assessed by radionuclide angiography and during cardiac catheterization.

CARDIAC PERFORMANCE DURING EXERCISE

Normal Response

The ability of the cardiovascular system to respond to the increased metabolic demands which occur during exercise determines its functional capacity. During dynamic exercise the cardiovascular system must increase the rate of oxygen transport to the working muscle to match the increase in peripheral oxygen demand and systemic oxygen uptake (9,77,78). This is accomplished by an increase in blood flow to the working muscle and an increase in the oxygen extraction. The cardiac output increases in a linear fashion until maximal oxygen consumption and work capacity is approached at which time the cardiac output fails to increase (13,79). The increase in cardiac output observed in the normal subject is accomplished by an increase in heart rate and stroke volume (12,13,14). Heart rate increases in a near linear fashion until maximum heart rate and oxygen consumption is approached. It is generally accepted that during dynamic upright exercise stroke volume reaches a maximum value at a heart rate of 110-120 beat/min. This maximum value is preserved for the duration of the exercise (13). Only at maximum heart rate does stroke volume decrease by 3-5% in some individuals.

Heart rate and stroke volume are not independent of each other. As the heart rate continues to increase during graded upright exercise, the left ventricle must fill and eject more blood in less time. If the determinants of stroke volume that result in increased fiber shortening did not change during exercise, stroke volume would fall with increments in heart rate. Therefore, a number of mechanisms must be utilized for the stroke volume to increase and then be preserved at a maximum value when the heart rate is greater than 110 to 120 beat/min . Observations from experimental data indicate that in the upright position the stroke volume is increased by the utilization of both the diastolic and systolic reserve mechanisms in the normal subject free from cardiac disease (14,15).

The diastolic reserve represents the increment in fiber shortening due to an increase in fiber length (i.e. chamber dilation or increased ventricular filling). The limit to the diastolic reserve is set by the level of pulmonary venous pressure (15). The presence of a diastolic reserve mechanism and the role of the Starling mechanism has been demonstrated in upright exercise using both invasive and non-invasive techniques (35,80,83). Studies performed in the erect posture demonstrate an increase in the left ventricular end-diastolic volume during submaximal and maximal exercise with little or no change in the end-diastolic pressure (35,84), therefore indicating a compliant ventricle. This phenomenon is in contrast to the situation in patients with ischemic heart disease.

Considerable controversy as to the role of the Starling mechanism in the supine posture remains. It has been suggested that the normal left ventricle operates at or near its maximal diastolic volume during supine rest and no further increases occur at the onset of exercise in this position (33). However, recent studies using radionuclide angiography (80,81), echocardiography (82) and invasive studies (35) have questioned previous findings.

The systolic reserve mechanism represents the increase in fiber shortening due to increments in the contractile state and the reduction in the afterload (15). Consequently, the myocardium is able to shorten to a greater extent utilizing its end-systolic volume reserve. Enhanced contractility is exhibited during exercise in the intact heart by a decrease in end-systolic volume (80-82), an increase in the left ventricular ejection fraction of 5% or more (15,80,81,83) and an increase in the ejection rate (15).

A decrease in the afterload or the systemic vascular resistance also enhances systolic emptying (15). Systemic vascular resistance is lower in endurance athletes when compared to normal sedentary subjects during exercise (85). Further, both these groups have less vasoconstriction to non-working tissues than do cardiac patients both at rest and during exercise (85). The increased vascular resistance demonstrated by patients with heart failure may be due to an increased sympathetic tone which is apparent by elevated plasma nor-epinephrine levels at rest and during exercise (86). Cardiopulmonary receptors with unmyelinated vagal afferents may be important in the regulation of the circulation by reflexive alterations in the neurohumoral drive. These afferents exert a tonic inhibitory influence on the peripheral sympathetic nerve activity and indirectly on the arterial pressure and vascular resistance (87). Heart disease may result in an alteration of this tonic inhibitory influence resulting in an increased sympathetic outflow that can lead to changes in arterial pressure and the release of renin and vasopressin (87). The increased vascular resistance in patients with heart failure may also be increased due to increased vessel stiffness (see review 88).

Cardiac Patients

The normal stroke volume response during exercise in the upright position represents the utilization of both the diastolic and systolic reserve mechanisms. In patients with coronary artery disease, the cardiovascular response to dynamic exercise is dependent on the extent of the disease, the functional capacity of the remaining myocardium and the neurohumoral status. Cardiac output usually increases in response to increased oxygen demand. However, it is often reduced at submaximal and maximal levels of work and oxygen consumption when compared with normal subjects (85). Heart rate increases in a linear fashion during exercise. However, the maximal heart rate is also often reduced when compared to that of normal age matched controls as is maximum work capacity (85). The response of the stroke volume determinants during exercise in patients with coronary artery disease is variable (84). Although abnormalities in cardiac function may not be apparent at rest, utilization of the diastolic and systolic reserve mechanisms can be limited during exercise.

Assessment of left ventricular function in clinical practice, is generally done by using invasive or non-invasive techniques to evaluate the determinants of stroke volume at rest and during exercise. Left ventricular end-diastolic volume or pressure and end-systolic volume or pressure and stroke volume can be evaluated. Recently, ejection fraction, the ratio of stroke volume to end-diastolic volume, has received extensive clinical use as a measure of systolic performance. This ratio can be obtained non-invasively by radionuclide ventriculography at rest and during exercise in the semi-recumbant position. In subjects free of heart disease, the exercise ejection fraction usually increases 10 to 20% above the resting level (80,81,83,89,90,92). In patients with coronary heart disease, an increase, a decrease or no change in the left ventricular ejection fraction during exercise has been observed (90-93).

The cardiovascular response to exercise has been examined over the past 20 years in a number of pathological states. The selection of the patient groups studied is often based on their clincial status (i.e. patients with or without signs of ischemia , patients who have suffered a previous myocardial infarction, according to their coronary anatomy, or according to the New York Heart Association Classification).

Malmborg (1965), using the Fick Principle and pulmonary capillary wedge pressures, investigated the hemodynamic response during supine exercise in normal subjects and in patients with clinical signs of coronary artery disease (94). Measurements were taken at rest and after 5-6 minutes of exercise. Resting data was similar in the patient group and the control subjects. However, during exercise the patient group exhibited a higher mean heart rate, lower stroke volume, higher intraventricular pressure and a higher systemic resistance than the control subjects. Individual data demonstrated a spectrum of stroke volume responses to increasing heart rates within the patient group with some being similar to that of the control group.

In 1967, Epstein et al using the Fick Principle investigated cardiac performance in a group of patients with various cardiac disorders including coronary artery disease and valvular disease (95). Although the data was pooled and presented as mean values, the individual stroke volume response during exercise appeared to be variable. In some patients the stroke volume appeared to drop at the onset of exercise. Another group of patients appeared to increase stroke volume at low workloads, on the other hand, during more strenuous exercise the stroke volume decreased. A small number of patients had a stroke volume response that was similar to that of the control group. Clausen et al (1970) reported similar findings in patients with coronary artery disease (96).

With the development of radionuclide ventriculography for assessing the ejection fraction, numerous investigators in the past decade have evaluated the change in this parameter at rest and during exercise as a means of defining left ventricular function (89,90). Investigations usually classify the ventricular function of patients with coronary artery disease according to their ejection fraction response to exercise: (i) Those patients who demonstrate a normal response (i.e. an increase in ejection fraction equal to or greater than 5%). (ii) Those patients who fail to increase their ejection fraction 5%. (iii) Those patients who demonstrate a fall of greater than 5% in the ejection fraction (89-92).

Several investigators, using the above method for assessment, studied left ventricular functional response during exercise in cardiac patients who experience signs of ischemia during exercise (i.e.

exercise-induced regional wall motion abnormality, angina and/or ST segment depression) (89,90,97-103). The left ventricular end-diastolic and end-systolic volumes were frequently assessed in the same studies. A decrease in exercise ejection fraction was usually observed (89,90,98,99,100-103). These patients exhibited usually an increase in the end-diastolic volume and a disproportionate increase in the end-systolic volume resulting in either a decrease or no change in the stroke volume at peak exercise when compared to the resting value (99,101-104). The ejection time was decreased while the ejection rate did not change from rest to peak exercise in patients who exhibited ischemia (99). Impaired left ventricular emptying was apparent during exercise only (99).

Investigators have also examined left ventricular function in post myocardial infarction patients without exercise-induced ischemic changes (100-101). End-diastolic volume increase while end-systolic volume decreased, increased slightly or did not change during exercise (99). The end-systolic volume at peak exercise was significantly less in the patients with scar tissue than in patients who exhibited ischemia (99-101). The ejection fraction did not change from rest to maximal exercise (100); however, variability was often noted with some exhibiting a normal response (101). Ejection time decreased while a slight increase was observed in the ejection rate from rest to peak exercise in these patients (99).

Other investigators examined patients who were selected according to the extent of coronary artery disease (102,104-107). Tan et al examined the hemodynamic response in post infarction patients with isolated occlusion of the left anterior descending artery (Group A) and those with 2 or 3 vessel disease including total occlusion of the left anterior descending artery (Group B) (105). The data at rest and during mild exercise was similar between the two groups. However, at peak exercise, Group B exhibited a significantly larger end-diastolic and end-systolic volume and a lower stroke volume than Group A. A decrease in peak ejection fraction was also noted in Group B whilst Group A exhibited no change in the ejection fraction at peak exercise when compared to resting values (105). Similar results have been reported by others (102,106) in patients with multivessel disease and single vessel disease. Leong et al studied patients with either proximal or distal lesions in the left anterior descending artery (105) They reported a significant decrease in the ejection fraction and a larger left ventricular end-systolic volume from rest to peak exercise in patients with a proximal lesion of the left anterior descending artery.

Ehsani et al (1984) studied left ventricular function in post infarction patients who were able to attain a true maximum oxygen consumption (108). These patients did not have clinical signs of ischemia during exercise. Results indicate that the change in ejection fraction was again variable. In patients who had an abnormal ejection fraction, the end-systolic volume was increased significantly. In the patients with a normal ejection fraction response, end-systolic volume decreased during exercise. Evidence of ischemia (i.e. abnormal regional wall motion) were not monitored in this investigation.

The above studies indicate that submaximal exercise provides valuable information on left ventricular function in patients with coronary artery disease. The investigations also suggest that the presence of functional ischemia can be assessed during exercise by the development of abnormal hemodynamic changes. Further, development of abnormal left ventricular function during exercise is a more sensitive measure of ischemia than either clinical symptoms or electocardiographic changes. In addition, the degree of abnormality can be related to the extent of myocardial ischemia (102).

In addition to the above investigations, patients with left ventricular dysfunction (defined as a resting ejection fraction of less than 40%) also exhibit cardiovascular responses to exercise that cannot be predicted by their resting data (7,8). In this group of patients, the end-diastolic volumes or pressures increase during exercise. Some of these patients exhibited an increase in stroke volume and stroke work during exercise while others exhibited a decrease or a failure to increase their stroke volume and stroke work during exercise (7,8). In patients with a history of ischemic heart disease and left ventricular dysfunction at rest, the ejection fraction was usually abnormal during exercise (8).

Weber et al have studied patients with chronic stable heart failure in classes I to IV of the New York Heart Association criteria (108). Patients were graded according to the maximum oxygen consumption attained. Pulmonary capillary wedge pressures (Swan Ganz catheter) and cardiac output (Fick Principle) were measured at each stage of exercise on the treadmill. Although the patients were classified into 4 groups, 3 hemodynamic responses were observed: (i) Two patient groups exhibited a normal filling pressure at rest and during exercise with an increase in heart rate, stroke volume and cardiac output during exercise.(ii) A third group of patients exhibited elevated filling pressures during exercise and increases in stroke volume, heart rate and cardiac output. (iii) The fourth group exhibited elevated filling pressures during exercise, no significant increase in stroke volume, an increase in heart rate and an attenuated cardiac output during exercise. Resting cardiac output, heart rate and stroke volume did not differ between the groups. Resting filling pressures were elevated in Groups 3 and 4 when compared to Groups 1 and 2.

In summary, resting data does not predict the work capacity or the hemodynamic response during dynamic exercise in asymptomatic patients with or without left ventricular dysfunction at rest. Only during exercise is it possible to determine the functional capacity of the left ventricle. However most methods for determining the hemodynamic parameters of the stroke volume are either invasive or require radioisotopes and are not easily repeatable. In recent years, evaluation of left ventricular ejection fraction at rest and peak exercise by radionuclide ventriculography has become common practice. Clinically, the ejection fraction is used as an index of contractility and ventricular function and is relatively easy to obtain. However, the ejection fraction is sensitive to loading conditions and heart rate (73,75). Changes in ejection fraction depend upon alterations in both end-diastolic and end-systolic volumes. Since it is a ratio, reciprocal changes in the parameters influencing the ventricular volumes may mask an actual decrease in the pumping ability of the left ventricle (i.e. a decrease in stroke volume).

In addition, many studies have provided data at rest and at peak exercise only. Collecting data at one point only during exercise may result in missed information regarding the ability of the left ventricle to function under stress. Patients with poor pump function throughout exercise may exhibit a similar ventricular responses at peak exercise to those patients who develop ventricular dysfunction at higher workloads and heart rates. Subclassification of these groups of patients may be important for evaluating of the extent of the disease.

In the studies covered above, patient selection is often based on clinical criteria (coronary anatomy, clinical signs of ischemia during exercise, myocardial infarction etc.). Since ventricular function involves the summation of a number of complex factors, this method of patient selection may contribute to difficulty in the intrepretation of data. Selection of patient groups by ventricular function during exercise may be a more objective method of selection. In addition, this method of patient classification may be more useful in determining long term management.

During a routine exercise stress test, ventricular function is not evaluated. Although heart rate, blood pressure and clinical symptoms and electrocardiographic changes are assessed, these parameters cannot predict ventricular function. Knowledge of the stroke volume response to increments in heart rate may provide an objective method of determining ventricular function in patients with coronary artery disease. It is suggested that impedance cardiography may be a reliable method for obtaining this data.

REGULATION OF THE CIRCULATION DURING EXERCISE

The factors that regulate cardiovascular performance during exercise include the determinants of myocardial function (i.e. preload, afterload, contractility and heart rate) and the peripheral vascular function. During the stress of exercise, these factors are coordinated by the sympathetic nervous system to ensure an adequate blood flow and delivery of oxygen to the working muscle. At the onset of exercise there is a withdrawal of parasympathetic nervous control and release of norepinephrine and epinephrine via the sympathetic nervous system (see review 110).

Plasma concentrations of both norepinephrine and epinephrine increase proportionally to the intensity and duration of exercise (110). In normal subjects and patients with ischemic heart disease, plasma norepinephrine concentration correlates closely with the pulmonary arterial oxygen saturation (112,113). Mixed venous oxygen saturation, a measure of the aerobic metabolic state in tissues, reflects the ratio of oxygen consumption to the cardiac output delivered to the working tissue while plasma norepinephrine concentration reflects the response of the sympathetic nervous system. In one study, when 100% oxygen was inspired during exercise the increase in plasma norepinephrine concentration was reduced by 25% in normal subjects (113). Such results suggest that the concentration of dissolved oxygen or some related factor may be important in the regulation of norepinephrine release during moderate to heavy exercise. Norepinephrine release in skeletal muscle continues throughout exercise when vasodilation is maximal (110,114). The mechanism of this release remains unknown.

Muscle Blood Flow

Increased sympathetic nervous activity and the withdrawal of parasympathetic activity during exercise results in an increased cardiac output and an increased perfusion pressure to the working tissue. Blood flow is directed away from the splanchnic area, kidneys, and non-working skeletal muscles due to an increased arteriolar resistance while vasodilation occurs in the working tissue (115). The degree of redistribution of the cardiac output is proportional to the relative workload undertaken (115). In the exercising muscle there is probably competition between the vasoconstriction mediated by the sympathetic system and vasodilation. However, the local influence of vasodilating metabolites overrides the vasoconstricting influence of the sympathetic nervous system in the working muscle in normal subjects (114,116). There is some evidence to suggest that this may also be the case in patients with heart failure (117).

At the onset of exercise, the increase in blood flow to the working tissue is very rapid (118). Some investigators suggest that nerves may be responsible for this rapid increase of blood flow at the initiation of exercise and for the first 30-40 seconds of exercise (118). However, neither the connection with the sympathetic nervous system, nor the character of either the transmitter or the means of activation of these nerves are clear (114). The main regulatory mechanism of muscle blood flow is the metabolic demand with metabolic factors contributing to the vasodilation during exercise which lasts longer than a few seconds (118).

Blood flow in skeletal muscles at rest differs with the different type of muscle fiber, the species and under different experimental conditions (114,119). During exercise, studies in a variety of muscles in rats running at different speeds and duration have indicated that the increase in flow clearly followed the pattern of recruitment of different fiber types (120,121).

To investigate the nature of the vasodilating agents in skeletal muscle, Cotterrell and Karim (122) observed the effects of adenosine and its analogues on arterial and venous resistance. Sympathetic stimulation produced an increased arterial resistance. With the infusion of adenosine, dilatation of the arterial resistance vessels resulted. Neither the purine or pyrimidine nucleosides nor inorganic phosphate had any effect on the resistance vessels. ATP exhibited a more potent vasodilatory effect than did adenosine in this experimental model.

Recently, Hudlicka (1985) has reviewed the regulation of muscle blood flow during exercise (114). In this review, studies presented suggested that a number of factors may initiate and maintain functional hyperemia in the working muscle. This review suggested that potassium may mediate primarily the vasodilation which occurs in mixed or predominantly glycolytic muscle while inorganic phosphate (Pi) may be involved primarily with vasodilation during short-lasting contraction in oxidative muscle and may act in accordance with a low pH. Adenosine, on the other hand, may play a major vasodilating role in long-lasting contractions in highly oxidative muscles. Hudlicka states that it is unlikely that one substance alone would be responsible for functional hyperemia in all fiber types and during exercise of differing intensity and duration (114).

The factor or factors involved in functional hyperemia during exercise in the intact animal and man remain controversial. At the onset of exercise, nervous control of functional hyperemia has not been ruled out (118). During exercise that lasts for longer an a few seconds, accumulation of metabolites probably accounts for the maintainance of vasodilation. The type of metabolite that leads to a reduction in arteriolar resistance most likely differs with the type of muscle fiber involved in the activity, the duration of the activity and the fitness of the subject (120,121) and probably results from several factors (114).

Control Mechanisms

The cardiovascular changes that occur during exercise are mediated by the sympathetic system which is controlled by the nervous system via a central command (see review 11,123). The central command appears to be primarily modulated by afferent fibers originating in the contracting muscle (11,123). The baroreceptors and receptors in the cardiopulmonary region also contribute to the regulation of blood pressure but their role is presently uncertain (11). The way in which the sensed variables and the integration of this information into an effective efferent response also remains unclear. It is believed that normal muscle activity is initiated by centers in the cerebral cortex. These centers and the information coming from the periphery have direct input into the areas of the brain stem that control the cardiovascular system (11,123).

The output via the central command coordinates the cardiovascular response to match the increased metabolic requirements. The consequence of this output is an increased sympathetic drive to the heart (increased heart rate and contractility) and blood vessels (increased resistance).

The afferent impulses from the skeletal muscles that have been implicated in causing the cardiovascular effects are transmitted by Group III and IV fibers (123). These fibers ascend in the spinothalamic tracts to the cardiovascular centers in the medulla. Some may be involved in reflexes at the spinal level. Ventral root stimulation (124,125) or direct muscle activation (126) have been shown to result in an increase in cardiac output, an increase in mean arterial pressure but no change in the total peripheral vascular resistance. In addition a sustained tetanic muscle contraction has been shown to result in an increase in the contractile state of the left ventricle (127), an increased heart rate and a change in the distribution of blood flow (i.e. increased flow to the contracting muscle and decreased flow to the kidney, resting muscle, skin and gut) (124,125).

Group III and IV afferent fibers are believed to be ergometric and are activated by muscle stretch or contraction. Group IV also respond to noxious stimuli (123). During exercise, the stimulus is probably muscle stretch, contraction or some biochemical product produced as a result of the increased metabolic rate (11,123). Evidence suggests that a release of bradykinin or potassium may stimulate the Group III and IV afferent fibers as the cardiovascular exercise response (increased heart rate and increased arterial pressure) appears to parallel potassium release (11). The heart rate and blood pressure response can be elicited by increasing the interstitial concentration of potassium with an intraarterial potassium infusion (11). However, conclusive evidence as to the mechanism of the reflex-induced alpha-adrenergic vasoconstriction remains elusive (123).

The regulation of blood pressure during exercise is not completely understood. Melcher and Donald (1981) found a normal arterial blood pressure response during light and severe exercise when either the carotid baroreceptors or the aortic and vagal cardiopulmonary receptors were intact (128). When all 3 systems were inoperative, arterial pressure fell at the start of mild exercise and remained depressed throughout the exercise. With aortic and cardiopulmonary reflexes intact, the shape of the curve was unchanged during exercise but the curve was displaced upward in response to increased carotid sinus pressure, indicating that the carotid baroreflex is "reset" during exercise and operates around a high mean arterial pressure (128). This new operating point varies proportional with the intensity of the exercise. Investigations have been done in conscious dogs to examine the ability of carotid baroreceptors to regulate arterial pressure during graded exercise in the chronic absence of the aortic baroreflex (129). Under these conditions and with carotid sinus isolation, investigations suggested that the arterial baroreflex function during exercise to prevent the reduction in pressure at the onset of exercise and to prevent an excessive increase in pressure during and after moderately severe exercise. The arterial baroreflexes appear to govern the total systemic vascular resistance during and after exercise, whereas heart rate and cardiac output are unchanged by the interruption of the arterial baroreflexes.

The role of the cardiopulmonary receptors during exercise is also not known. Activation of the afferent vagal fibers in the atria, ventricle or pulmonary artery results in an inhibition of the sympathetic efferent activity and a reduction in heart rate and blood pressure (see review 130). The mechanosensitive vagal receptors in the ventricle can be activated by increased myocardial tension due either to an increased diastolic volume or to a sudden decrease in venous return whereas the atrial C fibers are usually activated by increased stretch of the atrial wall. The chemosensitive vagal C fibers respond to prostaglandin and bradykinin which are released during hypoxia, ischemia and an increased preload. Whether these receptors buffer the blood pressure rise during exercise is at present unknown.

The afferent sympathetic fibers originating in the heart are activated by stretch of the receptive fields and by noxious stimuli such as lactic acid and bradykinin resulting from myocardial ischemia and coronary occulsion (see review 130). Stimulation of these afferent fibers generally results in an increased arterial pressure and heart rate. These cardiovascular effects result from an increase in the sympathetic efferent activity and possibly a reduction in vagal efferent activity. Whether the cardiopulmonary afferent fibers are operative during exercise and can modulate the central command remains unknown.

Animal models of heart failure exhibit attenuation of both the cardiac (131) and arterial baroreceptor (132) reflexes. Blunting of the arterial receptor reflexes may be related to changes in the vascular wall. The desensitization of the atrial receptors demonstrated in heart failure may be due to excessive stretch and decreased compliance of the atria and degeneration of afferent nerve fibers (132). An inappropriate reduction in cardiac vagal afferent activity may result in a failure of the normal attenuation of the efferent sympathetic nervous system which may partly explain the exaggerated sympathetic response during exercise in patients with heart failure (131).

IMPEDANCE CARDIOGRAPHY

Most methods of measuring cardiac output, such as dye dilution and the Direct Fick Principle, require sterile invasive procedures which can not be used repeatedly. It is often necessary to follow cardiovascular function in patients over months or years to determine prognosis and therapy. This requires an easily repeatable method which is acceptable to the patient. Impedance cardiography may be such a method. It has received increasing use and attention in the past decade. It is a non-invasive, atraumatic method of measuring stroke volume and heart rate and hence cardiac output. The technique involves placement of four electrode bands around the neck and thorax. A weak high frequency alternating current (4ma and 100KHz) is passed through the outer two electrodes. The constant alternating current is so weak that it is imperceptible to the subject and the frequency is so high that it is incapable of stimulating the heart (18).

Theoretical Basis

Ohm's law describes the interrelation between the current, voltage and impedance in any electrical circuit:

$$V = I \times Z \qquad (1)$$

Voltage (V) is the potential difference across the circuit. It can be defined as the amount of energy required to separate the electrical charge. The flowing current (I) in the circuit represents the speed at which the electrical charge is allowed to return to the basal state. The impedance (Z) represents the opposition to the flow of this current along the circuit and is determined by the material of an electric field. Impedance describes the resistance of an alternating current. The total resistance of blood in an artery (Rb) varies directly with the length of the conductor (L) and inversely with the cross-sectional area (A) of the conductor (133) and can be expressed by:

$$Rb = \rho \times L/A \qquad (2)$$

where ρ = the electrical resistivity of the blood (17,133).

Ohm's law is only valid if the current, potential difference and the impedance are considered in the same vectorial direction. To maintain this condition the sensing electrodes are placed parallel to the lines of current flow. Since a constant current is applied in the method under discussion, changes occurring in the detected voltage reflect the changes in the impedance between the sensing electrodes (17,133).

Electrical conduction through biological tissues is ionic in nature. The extracellular and intracellular fluid are composed of water containing ions which possess a charge and will migrate in the presence of an electric field. Various tissues within the electrical field display different conducting characteristics depending on their structure (i.e. the size and shape of the cells, the density of the cells, the ionic permeability of the membranes, the orientation of the cells and the distribution of a particular type of tissue) (134). The application of a high frequency alternating current results in a rapid reversing motion of ions. Under this situation, cellular membranes do not have time to collect ions on their surfaces therefore current flow becomes less affected by the membrane characteristics. However, the effect of the membrane is not eliminated entirely and the collection of ions at these barriers exhibit the properties of an electrical capacitor. The electrical current is impeded by the tissues and blood in the thorax. Any physiological change in the electrical field will result in a variation in conductivity. Contribution of the heart-synchronous impedance signal may be expected from the resistance variations in the long and large blood vessels which run parallel to the electrical field (17,133).

Historical Review

The variations in body impedance to high frequency electrical current ocurring during the cardiac cycle has been known since the beginning of the century (Cremer 1907) (133). In 1932 Atzler and Lehmann observed electrical impedance changes synchronous with cardiac activity in human subjects (133). These investigators used two insulated plates of a 100 megahertz oscillator. Using a tetrapolar electrode system Nyboer et al in 1940, passed a high-frequency signal across the human chest from a constant-current sinusoidal generator and observed changes in the thoracic impedance which coincided with the electrocardiogram and the heart sounds (135). In 1960 Nyboer then studied the impedance changes in a cylindrical volume of tissue which was perfused with a pulsatile arterial blood flow (136). The electrical impedance fell when blood flowed into the segment being examined and increased during the period of no flow or during run off. Nyboer converted the impedance measurement to blood volume measurement. He postulated that the fall in impedance during systole could be considered as an additional impedance that was placed in parallel with the basal impedance (Zo). Kubicek and co-workers used the formula ($\Delta V=\rho L^2 \Delta Z/Zo^2$) developed earlier by Nyboer along with a four electrode plethysmograph for the measurement of stroke volume (18). Nyboer developed this formula independently by calibrating impedance changes with different amounts of saline (17,135,136). He demonstrated a linear relationship between volume (V) and electrical conductance (Gb).

$$V=\rho b \times L^2 \times Gb \qquad (3)$$

where ρb= the electrical resistivity of the blood.

Since Rb=1/Gb, the above equation corresponded to the equation developed earlier by Bonjer (138) who derived a relationship between resistance of the blood and the volume of the artery (V):

$$Rb=\rho b \times L/A \qquad (4)$$

Where Rb= resistance of arterial blood; b= resistivity of blood; L=length of the artery and A= the cross-sectional are of the artery. The volume of the artery is (17):

$$V= L \times A \quad \text{or } A = V/L \qquad (5)$$

Substituting formula 5 in 4:

$$Rb=\rho b \times L^2/V \qquad (6)$$

A change in arterial volume (ΔV) will result in a variation in the resistance of the artery (ΔRb). Therefore:

$$\Delta V=\rho b \times L^2/\Delta Rb \qquad (7)$$

This formula is equivalent to formula 3. Nyboer considered the impedance system to be essentially a plethysmogram which measures a variation in volume. By experimentation he concluded that a change in the overall conductance in a tissue segment is a linear function of the volume of blood added to the segment under consideration (137), therefore:

$$\Delta V=\rho b \times L^2 \times \Delta Gb \qquad (8)$$

The thorax can be considered a conductor composed of 2 parallel conducting paths, through the blood and through the tissue. The resistance of the tissue (Rt) and blood (Rb) make up the total resistance (Ro), therefore:

$$1/Ro= 1/Rb + 1/Rt \qquad (9)$$

An additional amount of blood entering the thorax alters the resistance of blood (Rb') and the total resistance becomes (Ro + Δ R), therefore:

$$1/(Ro+\Delta R)= 1/Rb' + 1/Rt \qquad (10)$$

Rearranging equation 9 and substituting in equation 10, a small change in the overall resistance (R):

$$\Delta G=\Delta(1/R)\approx -\Delta R/R^2 \qquad (11)$$

The effect of the volume variation during ejection is:

$$\Delta V \approx -\rho b \times L^2 \times \Delta R/R^2 \qquad (12)$$

Since impedance can be substituted for resistance for an alternating currents:

$$\Delta V = \rho b \times L^2 \times \Delta Z/Z^2 \qquad (13)$$

Kubicek and co-workers used this formula, developed by Nyboer together with a four electrode plethysmograph for the measurement of stroke volume (18). Cardiac output was calculated by an extrapolation procedure. The slope of the Δ Z wave was extrapolated to the instant of the closure of the pulmonary valve. When compared with the Fick method, the impedance cardiac output was about 13.7% higher. The method was difficult to use and prone to error. Therefore to improve accuracy and to simplify the calculation of stroke volume, the slope of the impedance curve was determined using the rate of change of the impedance (dZ/dt) (139). This value was then multipled by the right ventricular ejection time (T) to determine the change of impedance. Therefore,

$$V = \frac{\rho b \times L^2 \times dZ/dt \times T}{Zo^2} \qquad (14)$$

The development of this formula and the first commercially available impedance cardiograph by Kubicek and co-workers initiated increased interest in the technique for laboratory and clinical use. Formula 14 was used for the calculation of stroke volume in the present series of investigations.

The method and formula developed by Kubicek (18,139) for the measurement of stroke volume was based on the simple assumption that blood and fluid in the thorax results in a decreased electrical impedance. The technique has been shown to correlate reasonably well with invasive methods such as the Fick and dye dilution methods (17,133). However, the question as to why a change in the thorax electrical impedance occurs which is associated with the cardiac cycle has not been answered. The lack of this knowledge has caused reservations in acceptance of the method. During systole many events occur in sequence and simultaneously. The predominate hemodynamic event or events which contribute to the change in electrical impedance is not known. Understanding of the physiological origin of the impedance events is necessary before the meaning of a change in the waveform can be intrepreted or a complete description of cardiac function can be appreciated.

Origin of the Impedance Signal

Many investigations have been undertaken in an attempt to understand the physiological origin of the impedance events. Initial investigators suggested that the change in impedance may be due to volume changes in the heart (136). Later Bonjer et al demonstrated in a perfusion experiment on the hind limb of a dead animal and by insulating the heart of a living animal that the main component of the impedance variation originates from the rhythmic volume change in the blood content of the vessels (140). Kubicek, in 1964, (18) and Kinnen (141), using band electrodes suggested that the lung was the principle cause of the impedance change. However, Witsoe and Kottle (142) in a later study examined a dog which developed left ventricular mechanical alternans. They concluded that the aorta was probably the source of the impedance change as did Harley who studied patients before and after closure of atrial septal defects (143). Geddes and Baker, in 1972, injected saline into the right and left ventricle and observed that the volume changes of the ventricle did not cause a significant change in the impedance (144). Left ventricle ejection was associated with a greater decrease in impedance while the right ventricle ejection made a small contribution (144,145).

Ito et al (146) perfused the aorta and the pulmonary artery of a dog with a controlled sinusoidal or pulsatile flow. Stroke volume was calculated using Kubicek's method and by an electromagnetic flowmeter placed in the aorta and pulmonary artery. Each vessel was occluded independently and the change of impedance was recorded. Results indicated that the main component of the transthoracic impedance waveform originated from systemic blood flow and not pulmonary blood flow.

In 1978, Patterson and co-workers (147) examined the change in impedance resulting from infusion of blood into various isolated segments of the great vessels and the heart chambers. Results indicate that the impedance changes were sensitive to volume changes in both the right atria and aorta with the ventricles contributing only a small amount. The investigators concluded that the volume changes in several of the intrathoracic cardiovascular structures are likely to be involved in the impedance change. Impedance contributions from the blood volume changes in the venous system were also reported by others (17, page 98). During an induced cardiac arrest a small decrease in impedance occurred after cessation of ventricular ejection. This was attributed to an increase in venous blood pressure due to an increase in venous blood volume in either or both the systemic and pulmonary veins. Geddes and Baker demonstrated a similar decrease in impedance following the injection of saline into the aorta and the inferior vena cava (145).

In 1979 Sakamoto et al investigated the relationship between the waveforms and the circulation in the thorax (148). When the impedance waveforms were measured in the vicinity of the heart, an increase in impedance was exhibited during early systole. The impedance decreased in the vicinity of the aortic arch. This opposite effect of the heart on the impedance has been reported by others (149). They concluded that the change of blood volume in the aorta and in various organs especially the heart contributed to the waveform. This study suggested that important information regarding the hemodynamics in various organs can be obtained from the impedance waveform by the appropriate arrangement of electrodes (148).

The impedance changes in all the previous studies were interpreted as being due to blood volume variations and the investigators attempted to localize these volume changes. More recently, it has been suggested that the impedance change may be the result of blood flow dependent changes in resistivity (17). The impedance of flowing blood changes with the change of flow velocity due to the orientation of red blood cells (17,150). This was demonstrated by several investigators who found that a pulsatile flow of blood through a rigid tube resulted in an change in impedance (17). The impedance wave differed when equal volumes of saline was used and compared with blood (17). In a later experiment, it was demonstrated that a decrease in the hematocrit resulted in a decrease in the impedance variation in a rigid tube (17). Further, the impedance variation disappeared when a stroma-free hemoglobin solution was infused into a dog (151).

A number of studies have compared impedance cardiography with the existing clinical techiques which evalute left ventricular function. During simultaneous recordings of the apexcardiogram and impedance cardiogram, the dZ/dt wave (i.e. maximum change in impedance) coincided with the systolic peak of the apexcardiogram (133, page 37-38).

The M-mode echocardiogram of the ventricular cavity and of the aortic root were recorded simultaneously with an impedance cardiograph (133, page 38). The systolic portion of the dZ/dt tracings occurred only when the aortic valve was open and the X-point of the impedance cardiograph recording occurred immediately following aortic valve closure while the O-wave of the dZ/dt recording corresponded to mitral valve opening.

Using simultaneous recordings of the electrocardiogram, dZ/dt wave and the ballistocardiogram, Mohapatra and Hill, demonstrated that the I-wave or the rapid ejection from the ventricles as recorded by the ballistocardiogram coincided in time with the dZ/dt systolic peak (152).

Lababidi et al (1970) examined the components of the first derivative of the thoracic impedance (dZ/dt) and demonstrated that the sharp demarcated points occurred synchronously with the first heart sound (B-point), aortic closure (x-point), pulmonic closure (Y-point),

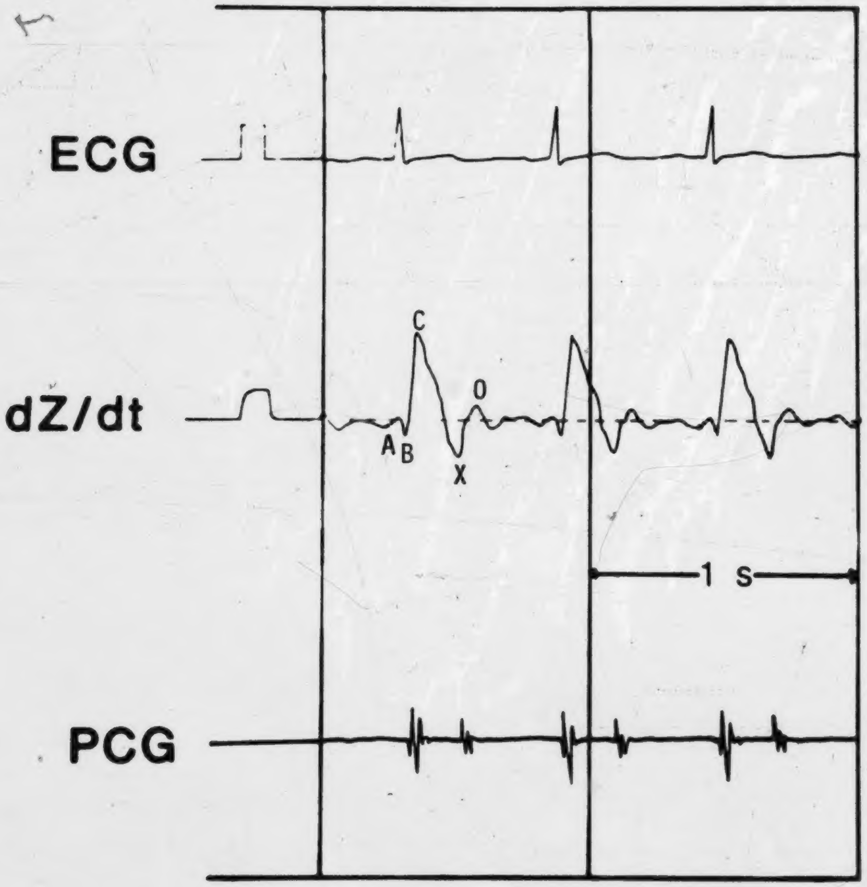

Diagram 2

The first derivative of the thoracic impedance cardiogram and its relationship to the cardiac cycle: A-wave, corresponds to the atrial systole; B point, coincides with the main portion of the first heart sound and appears immediately after the aortic valve opens; C-wave, corresponds to ventricular systole; X point, appears immediately after the aortic valve closes and coincides with the second heart sound; O-wave, corresponds to mitral valve opening and primarily occurs during the rapid filling phase.

mitral opening snap (O-point), the third heart sound (Z-point), and the fourth heart sound (A-point). The B-point designates the onset of left ventricular ejection (see Diagram 2). These investigators (153) and others (154) concluded that the first derivative of the impedance tracing may be used for the timing of the intervals of the cardiac cycle.

Determination of Stroke Volume

The impedance cardiograph developed by Kubicek et al (1966) allows for the direct recording of impedance changes, the first derivative of the impedance change, the heart sounds and the heart rate. Stroke volume is calculated using the formula (18,139):

$$SV=\frac{\rho \times L^2 \times dZ/dt \times T}{(Zo)^2} \qquad (15)$$

where ρ = resistivity of blood, L= distance between the inner pair of electrodes, Zo= mean thoracic impedance in ohms, dZ/dt= maximum rate of change of the impedance occurring during the cardiac cycle in ohms/second, and T= the left ventricular ejection time in seconds.

However there is no standard method for determining the values in the above formula. In attempts to correlate impedance cardiography values more closely with those obtained by invasive techniques, investigators have empirically used various methods for determining the values needed for calculating stroke volume.

A knowledge of the electrical resistivity of the patient's blood is required. Many investigators have used fixed values of 150 or 135 ohm-cm for resistivity (139). However, during exercise both body temperature and hematocrit rise. Therefore under conditions where hematocrit may be changing investigators have examined blood resistivity. Rosenthal et al (1948) reported a relationship of hematocrit and resistivity of $p=62.9 \exp^{(0.0195 \text{ Hct})}$ (155). Mohapaptra et al (1975) related resistivity to hematocrit where $p=68 \exp^{(0.025 \text{ Hct})}$ for neonates and adults with normal fresh blood (156). Geddes et al found resistivity to increase with increasing hematocrits and provided the relationship of $p=53.2 \exp^{(0.022 \text{ Hct})}$ for the calculation of the resistivity factor (157). When hematocrit is accounted for in the resistivity factor, accuracy in the cardiac output values obtained by impedance cardiography have been improved when compared to standard techniques (17).

The length (L) between the 2 inner electrode bands in a tetrapolar arrangement exerts an influence on the magnitude of the calculated stroke volume. A variation in the calculated stroke volume has been observed with a change in the position of the inner pair of electrodes (17,133). Investigators recommend that electrode 2 should be placed around the base of the neck and electrode 3 placed at the level of the xiphisternal joint, a prominent anatomical landmark which assists in the consistent location of this electrode. Both the shortest distance between the 2 inner electrodes (158) and the mean of the mid anterior and posterior distance (18) have been used as the length (L) value in an attempt to increase the accuracy of the stroke volume measurement.

Determination of the left ventricular ejection time (T) from the impedance cardiogram was shown to be highly correlated with the ejection time obtained from the carotid pulse tracing (154). Kubicek (159) proposed the value for "T" be measured from a point at 0.15(dZ/dt) to the largest deflection of the second heart sound. Usually the zero-crossing of the dZ/dt tracing corresponding to the B-point is used for the commencement of ejection time (160).

The mean or basal impedance (Zo) across the thorax decreases in value with increased fluid in the intrathoracic cavity and increased on assuming the upright posture (17,133). In the presence of a pleural effusion, differences between the stroke volume values measured by the impedence cardiography and the flowmeter differed substantially and therefore Baker and Dennison (1975) have recommended caution in interpreting recordings under these circumstances (161). The mean impedance usually reads between 20 to 35 ohm in adults. During exercise in normal subjects, the Zo value usually remains constant while in patients with heart disease the mean impedance value may decrease (17).

Measurement of the first derivative of the change of impedance (dZ/dt) is generally measured from the baseline (18). However, some investigators have recommended using the start of the steep upslope of the dZ/dt waveform (B-point) for the baseline irrespective of its position relative to the calibration zero baseline when measurements were taken during exercise (162). This point is also used for the initial point when measuring left ventricular ejection time with the X-point or the second heart sound as the end point (153).

Validation Studies

Many investigators have reported an acceptable correlation coefficient between estimates of cardiac output obtained from impedance cardiography and a "standard" method (i.e. dye dilution, Fick technique, CO_2 rebreathing or electromagnetic flowmetry) (18,19,139,158-160, 163-178). However, a variation in the systematic error has been exhibited in a number of these studies (162,163,174,175). A number of investigators agree that impedance cardiography accurately reflects the magnitude of change in cardiac output and is therefore suited for repeated intrasubject evaluations (17,163,164). However, whether absolute values for stroke volume can be measured by impedance cardiography remains controversial (17). Some investigators have reported extremely poor estimates by impedance cardiography when compared to the "standard" method (163-166). However, many of these studies were reported earlier and used patients with valvular disease and shunts (165,166). A more complete review of the validation studies has been presented by Mohapatra (132) and Lamberts et al (17). Only a few studies have used the Direct Fick technique in the validation of the impedance cardiograph (169,170,175). Findings indicate that there was a good correlation between the two methods however all studies were done at rest.

The reported short term repeatability of the impedance cardiogram is comparable with that of the dye dilution method (165,166). Acceptable repeatability has also been reported over a 2 week period (179) and a 9 month period in normal active subjects (168).

Validation studies done at rest and during exercise have indicated that the cardiac output at rest and at low workloads correlated well with values obtained from the standard method (usually dye dilution or CO2 rebreathing) (162,168,171,173,177,178). Although cardiac output measured by impedance cardiography increased with increasing work and oxygen consumption, values were found to be extremely variable and lower than expected at heavy workloads and at maximum exercise (17,162,175,180,181). When the blood resistivity was accounted for during submaximal and maximal exercise, impedance cardiography provided a reliable and reproducible estimated of cardiac output (162,180,181). However, even with this adjustment, some investigators found that impedance cardiograph values remain lower during heavy exercise (17).

Dennison et al adjusted the technique by using the shortest distance between the 2 inner electrodes for the "L" value in addition to the adjustment for hematocrit (171). These investigators reported no significant difference between the cardiac output values obtained by impedance cardiography and the dye dilution technique during submaximal exercise.

Miles et al adjusted for hematocrit and used the heart rate at steady state exercise when calculating the cardiac output. Values were similar to the reported values for arm exercise by invasive methods (182). Kobayashi et al (180) and Fujinami et al (181) demonstrated an improved agreement with published data during submaximal and maximal work when blood resistivity was taken into consideration.

Edmunds et al, in addition to adjusting for the change in hematocrit, also measured the change in impedance using the steep upslope of the dZ/dt wave form (B-point) as the baseline. They also used the B-point when measuring the left ventricular ejection time. Results indicated that these adjustments resulted in an improved agreement with values obtained by the CO_2 rebreathing technique (162).

Most invasive techniques require the accumulation of data over 1 to 2 minutes and assume a constant value for stroke volume over this time period. Impedance cardiography estimates beat-by-beat change in stroke volume. To evaluate the accuracy of the beat-by-beat values of stroke volume when measured by impedance cardiography, Ebert et al compared this technique to measurements derived from left ventriculography (183). This study was done at rest during cardiac catheterization. The results suggested that stroke volume estimated by impedance cardiography provided a reliable estimate of the absolute stroke volume and the change in stroke volume.

In summary, impedance cardiography is a non-invasive method of measuring beat-to-beat variations in stroke volume. In the absence of left-to-right shunts and valvular insufficiency (17,165,166), impedance cardiography can provide both reliable and reproducible estimates of the cardiac output and stroke volume in man and animal.

It appears that impedance cardiography probably measures impedance changes that occur primarily in the aorta during ejection hence output from the left ventricle. However, the factors that contribute to this change in conductivity are not completely understood and further investigation is necessary. At present it appears that contributions from the systemic and pulmonary veins may also occur (17,143-148). It also seems likely that the velocity of blood flow and the orientation of the red blood cells may contribute to the genesis of the dZ/dt wave form (150,151).

There is a lack of validation of the impedance cardiogram using the Fick Technique as the reference method during exercise. Since this technique is considered the most valid one for measuring cardiac output, determination of the systematic error in the impedance method when compared to the Fick Technique during exercise would be of value. In addition, limited studies have been done during maximal exercise in normal subjects. If the method was found to have no systematic error or a constant error throughout the test when compared to the Fick Method and adapted to maximum exercise testing, the procedure may be more acceptable and more universally used. Application of the technique for use for patients with coronary artery disease in the cardiac rehabilitation is also lacking.

AIM OF THE PRESENT STUDY

This study was designed to evaluate the possibility of using Impedance Cardiography as a method to assess the stroke volume response to increasing heart rates during upright exercise in patients with ischemic heart disease. Impedance Cardiography is a non-invasive technique which will permit a large number of patients to be examined. Further, due to the nature of the technique, adaptation to the cardiac rehabilitation setting may have important practical implications.

Answers were sought to the following questions:

1. Is it possible to generate the stroke volume-heart rate profile and hence cardiac output accurately and reliably by a non-invasive technique?
2. Is it possible to generate normal stroke volume-heart rate profiles and cardiac output in endurance trained athletes?
3. Is it possible to generate a stroke volume-heart rate profile non-invasively in patients with known left ventricular dysfunction?
4. What is the stroke volume-heart rate profile in patients who have suffered an acute infarction about 2 months previously?

The general methods of this series of investigation will be outlined in Chapter II. Following this, questions 1 and 2 will be dealt with in Chapter III while questions 3 and 4 will be dealt with in Chapters IV and V respectively. Each of Chapters III, IV and V will commence with a short introduction regarding the particular problem, will include the results of the investigation and will conclude with a short discussion. Chapter VI will be a short discussion regarding the clinical and physiological implications of this series of investigations and will conclude with a number of future research questions.

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CHAPTER II

GENERAL METHODS

Measurement of Stroke Volume and Cardiac Output

The Minnesota Impedance Cardiograph Model 304A (Surcom Inc., Minneapolis) was used for measuring cardiac output in this series of investigations. Four bands of self-adhesive mylar-backed aluminum electrodes were placed around the neck and chest 30 minutes prior to the commencement of the study. Two were placed around the neck, 3 to 5 cm. apart. The third electrode was placed around the the trunk of the body at the level of the xiphisternum and the fourth was placed at least 5 cm below the third electrode. When connected to the impedance cardiograph, the two outer electrodes transmitted a constant sinusoidal alternating current (4ma RMS and 100 KHz) through the thorax and the changes in the transthoracic electrial impedance were detected by the two inner electrodes (Fig. 1A). Mean total impedance between the inner electrodes (Zo) was computed by and displayed on the Impedance Cardiograph. Simultaneous recordings of the rate of change of impedance through each phase of the cardiac cycle (dZ/dt), the electrocardiogram and the phonocardiogram were made on an ink recorder at a paper speed of 50 mm.sec (Model 2400S, Gould Inc., Cleveland). The heart rate, dZ/dt_{min} and the left ventricular ejection time (T sec) were obtained from the recordings as shown in Fig. 1B. Calculation of the stroke volume was made using the following equation (1):

$$\text{Stroke Volume} = \frac{\rho \times L^2 \times T \times dZ/dt_{min}}{Zo^2}$$

where, ρ = resistivity of the blood at body temperature as determined by ($53.2\ e^{0.022H}$) (2), H=hematocrit (%), L= average distance between the inner pair of electrodes measured at the anterior and posterior midline (cm), T=left ventricular ejection time (sec), dZ/dt and Zo were obtained and defined as described above.

Recordings were made at rest and during exercise with the sujects in the upright position or supine (during the cardiac catheterization study only) on a bicycle ergometer. It was found that movements caused by respiration and exercise introduced artefacts into the recordings. These artefacts were avoided by requesting the subject to stop all movements both at rest and at the end of each workload. The subjects were instructed of hold their breath at normal end-expiration and and to stop pedalling for about 5 to 10 seconds, while 6-10 cardiac cycles were recorded. All the calculations were based on 5 cardiac cycles. The subject then resumed exercise immediately after completion of the recording. Blood for the measurement of the hematocrit was obtained from the antecubital vein immediately following each recording.

Blood pressure was measured by a sphygmomanometer at rest and at the end of the second minute of each workload and after competion of the symptom-limited exercise test. A 12-lead electrocardigram was monitored continuously throughout the test.

Protocol for Exercise Tests in Patients

The patients performed exercise on the bicycle ergometer (Model No. 388, Cycle Ergometer Siemens Ltd.) in the upright position. All patients were familiar with the apparatus. The participants came to the exercise laboratory in a fasting state. The workload started at 30 watt and increased by 20 watt every 3 minutes until one or more of the following end points was reached: i) 85% of the predicted maximum heart rate, ii) chest pain, iii) electrocardiographic ST changes compatible with ischemia (i.e.>1 mm depression), iv) ventricular arrhythmias during exercise (i.e. PVC>10/min, multifocal PVC's, couplets or ventricular tachycardia, v) an abnormal drop in blood pressure or a failure of the blood pressure to increase over three consecutive workloads, vi) fatigue or shortness of breath, vii) dizziness (3).

Diagnosis of Myocardial Infarction

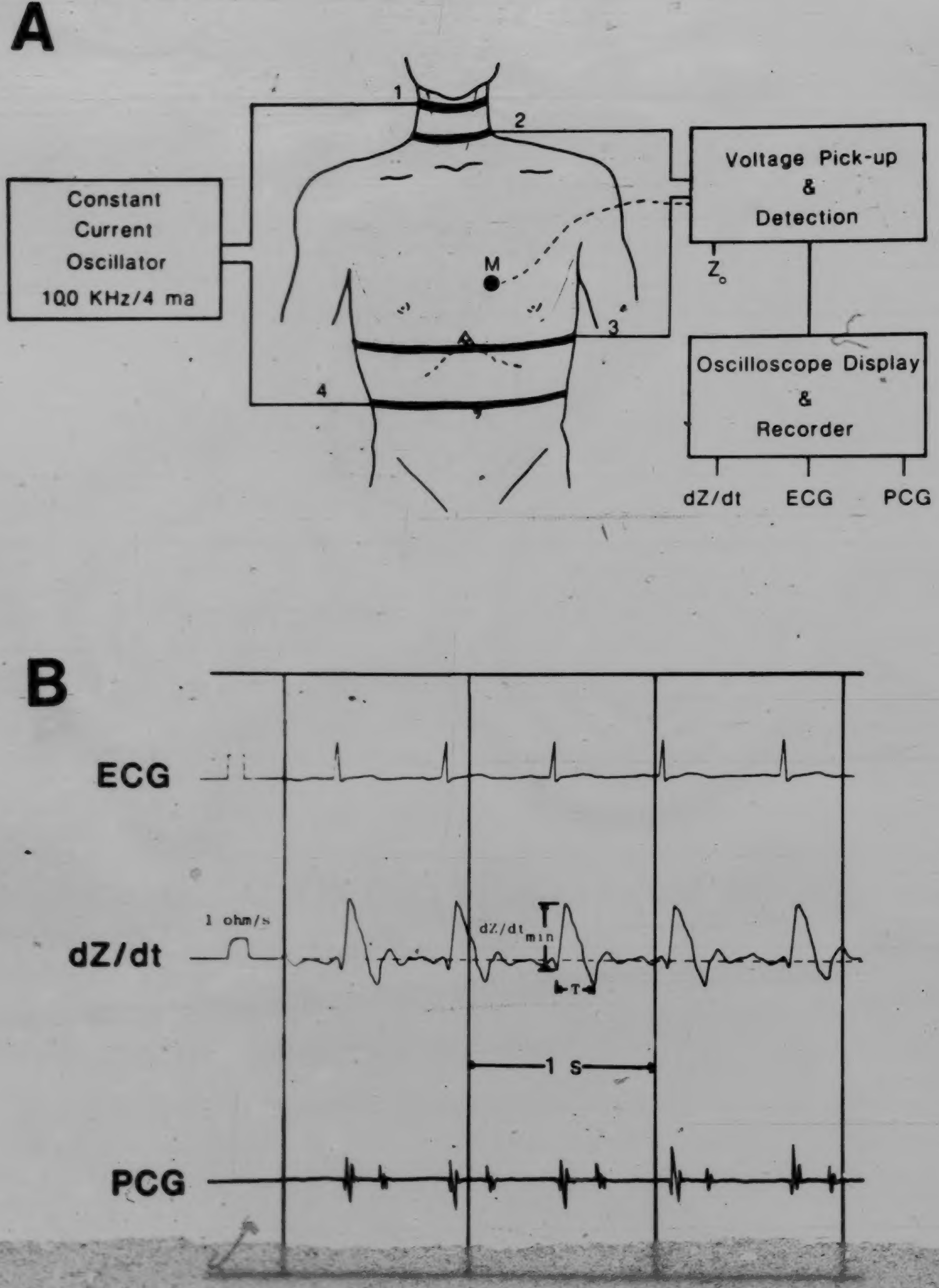
Myocardial infarction was diagnosed by the presence of two or more of the following: i) typical history of retrosternal chest pain, ii) electrocardiographic changes, and iii) elevation of cardiac enzymes (creatine kinase >105 iu/l and creatine kinase-MB >14 iu/l).

Figure 1A and B

A. POSITION OF THE ELECTRODES USED TO RECORD THE THORACIC IMPEDANCE CARDIOGRAM: Attachment of strip electrodes on a subject; electrodes 1 and 4 are connected to the constant current oscillator while 2 and 3 are used to detect changes in current. (Z_0 - average total transthoracic impedance, dZ/dt - rate of change of impedance, ECG - electrocardiogram, PCG - phonocardiogram, M - microphone placed on precordium).

B. TYPICAL RECORDING OF THE IMPEDANCE CARDIOGRAPH:

Typical impedance cardiogram recording with simultaneous ECG and PCG. Measurement of dZ/dt_{min} and ejection time T is as shown. Broken horizontal line shown with the dZ/dt record is the calibration base line.


A
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Constant Current Oscillator 100 KHz/4 ma
Voltage Pick-up & Detection
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Oscilloscope Display & Recorder
dZ/dt
ECG
PCG
B
ECG
1 ohm/s
dZ/dt
dZ/dt_{min}
T
1 s
PCG

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CHAPTER III

VALIDATION OF IMPEDANCE CARDIOGRAPHY[a]

Introduction

Resting hemodynmamic parameters have been shown to be an unreliable means of predicting exercise capacity (1) or cardiovascular response to exercise (2,3). Measurement of the cardiac output during exercise provides valuable information when assessing the functional capacity of the cardiovascular system in patients with cardiac disease. However, most methods used to evaluate cardiac output are invasive or require isotopes and are therefore not readily available to all patients nor are they readily repeatable. Impedance cardiography is a non-invasive method of obtaining cardiac output. Use of this technique may ensure frequent access to information regarding the ventricular response during both upright and supine exercise.

Beat-by-beat measurement of stroke volume and heart rate (hence cardiac output) can be obtained by this method (4). The procedure involves application of a small constant current (4ma 100KHz) across the thorax (5). The movement of blood parallel to this electric field, caused by the ejection of blood from the left ventricle, creates a change in the transthoracic impedance (6). The changes in the electrical impedance that occur during systole appears to be due to volume changes in the aorta due to left ventricular ejection (7,8). In addition the orientation of the erythrocytes in the flowing blood during ejection appear to contribute to the rate of change of the impedance (9). Only minor contributions appear to arise from the right ventricular ejection (10).

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[a] A version of this chapter has been published: Teo KK, Hetherington MD, Haennel RG, Greenwood PV, Rossall RE, & Kappagoda T. Cardiac output measured by impedance cardiography during maximal exercise tests. Cardiovascular Res 1985; 19:737-743.

Several investigators have attempted to validate the technique and there is general agreement that the procedure provides an acceptable measure of the cardiac output at rest and during submaximal exercise (11). Whether the method provides reliable and reproducible estimates of absolute or relative changes for cardiac output in humans remains controversial. Previous studies were usually done during supine exercise at relatively modest levels of activity (i.e cardiac outputs of less than 10 l/min) (12-16). Dye dilution or the CO_2 rebreathing techniques were usually used for comparison. Studies done at maximal exercise often resulted in an underestimation of the cardiac output (11,14).

When evaluating a new system of measurement it is necessary to determine the validity and repeatability of the method under study. First, the method should measure what it is intended to measure, that is, the cardiac output. The performance of the method during the actual study should be tested and the results should follow the expected physiological increases and decreases. Secondly, the source of error should be determined. Error may be due to the measuring instrument, the technique used in the data collection procedure or due to the observer or environment. The systematic error or constant error refers to the error due to some known or unknown influence that causes the score to lie in one direction (i.e. above or below the true value). The systematic error tests the inherent precision or accuracy of the method. To identify the systematic difference of the new method, it is necessary to calibrate all data obtained from the new method against that from a reference technique (i.e. Direct Fick Technique). Once the presence or absence of a systematic error is determined, plus any bias contributed by the observer and the collection technique have been controlled, it is necessary to determine the repeatability or random error of the new technique. Random error or the variability of individual measurements reflects the fluctuations due to chance and should be determined at a steady state and at short intervals. Finally, determination of long term reproducibility or repeatability should reflect how the technique will be used in practice.

The value of impedance cardiography as a method of measuring both stroke volume and cardiac output during exercise would be enhanced if it could be demonstrated that the measurements made were free of systematic error or demonstrated a constant error and one that was in the same direction when compared to the direct Fick technique. In addition, the acceptance of the technique would be enhanced if the measurements made were reproducible during maximal exercise. Therefore, the present study was undertaken to determine whether there was any systematic error in the technique when compared to the direct Fick method at rest and during exercise. Secondly, the random error of the technique was examined. Thirdly, the reproducibility of the technique was examined during conventional maximal exercise tests using the bicycle ergometer.

The study was performed in 3 separate stages:

1) Assessment of any systematic error by comparing simultaneous measurements of cardiac output by impedance cardiography and the direct Fick method.

2) Estimation of the short term random error by repeated measurements of cardiac output and stroke volume at rest and during "steady state" exercise.

3) Determination of the reproducibility of the method by comparing measurements made during two maximum exercise tests carried out one week apart on healthy endurance trained athletes.

4) Determination of the stroke volume-heart rate response during upright exercise in endurance trained athletes.

Methods

1) Estimation of the Systematic Error: Comparison of Impedance Cardiography and the Direct Fick Method

Comparison was done during cardiac catheterization in patients who were being investigated for angina pectoris. All patients were in normal sinus rhythm. Catheters were positioned in the main pulmonary artery (F7 Zucker Catheter, USCI) and in the descending aorta (F8 Pigtail Catheter, Cordis) for obtaining blood samples. Cardiac output was determined by impedance cardiography (as described in "General Methods") and by the direct Fick method, at rest and during supine exercise using a bicycle ergometer (Model 38B, Siemens Ltd). The level of exercise was selected on an individual basis for each patient, depending upon clinical status and exercise capacity as determined by a previous exercise test.

Oxygen uptake was measured during the 3rd and 4th minute and blood samples from the pulmonary artery and the descending aorta were collected at the end of the 4th minute. Impedance cardiography recordings were made immediately following the oxygen uptake measurements. Cardiac output was then calculated by the direct Fick method and by impedance cadiography.

Using the Fick Principle, cardiac output was calculated from the oxygen consumption and the arterio-venous oxygen difference. The oxygen consumption was measured using a continuous flow technique (17). Arterial and venous oxygen content was determined from blood samples taken simultaneously from the pulmonary artery and the descending aorta. Oxygen content of each blood sample was calculated from the measured percent oxygen saturation (Unistat Oximeter, Model No. 405805, American Optical Co.) and the theoretical oxygen carrying capacity. The latter was obtained by multiplying the hemoglobin concentration (gm/100ml) by 1.34 (ml 02/gm hemoglobin) (18). The amount of dissolved oxygen was calculated on the basis of the PaO_2 (19) and this quantity was added to the above value to estimate the total theoretical oxygen carrying capacity.

2) Estimation of the Short Term Random Error

This part of the study was performed in 4 healthy male subjects, (mean age 22.3 ± 2.3 years, SEM). The exercise was undertaken in an upright posture on a bicycle ergometer (Model 38B, Siemens Ltd). In each subject the cardiac output was measured according to the following protocol. First, four consecutive measurements were made during rest at intervals of 3 minutes. Next, each subject exercised for 12 minutes at 80W and the stroke volume and cardiac output were measured at the end of the 3rd, 6th, 9th and 12th minute. The subjects rested for 15 minutes and then exercised at a workload of 130W for another 12 minutes. Four measurements of cardiac output and stroke volume were made as above. In this way it was possible to obtain four measurements at 3 different steady states in each of the four subjects.

3) Reproducibility of Impedance Cardiography Measurements During Maximal Exercise

Six healthy young male athletes (mean age 26.2 ± 4.4 years, SEM) were studied. They were exercised in an upright posture on a bicycle ergometer (Model 38B, Siemens Ltd). The subjects were endurance trained athletes and were able to perform two reproducible maximum exercise tests in terms of maximum heart rate and oxygen consumption undertaken one week apart. Exercise workload started at 30W, increased to 50W, 80W and then in increments of 50W every 3 minutes up to the maximum exercise as indicated by a plateau of the oxygen consumption (20). Stroke volume, heart rate and cardiac output were measured at rest and at the end of each 3 minute stage of exercise up to the maximum level. Oxygen consumption was measured at each stage for 2 minutes just prior to the cardiac output determination.

Statistical Methods

1) The systematic error was assessed by comparing the Impedance Cardiography data with data obtained by the Fick method by means of a

least square regression analysis and by determining the correlat~~ion~~ coefficient (21).

2) The random error was expressed in terms of the coefficient of variation.

3) The reproducibility was examined by comparing the two measurements made one week apart using a least square regression analysis and by determining the correlation coefficient (21).

All group data were expressed as mean ± standard error of the mean. A "p" value of <0.05 was taken as the level of significance for the difference between groups.

Results

1) Assessment of the Systematic Error

A total of 40 measurements were made at rest and during supine exercise in 20 patients (for clinical details see Table I). A highly significant linear correlation between the measurements made by Impedance Cardiography and those made using the Direct Fick technique was found (correlation coefficient, $r=0.93$, $p<0.001$). The slope of the regression line and the intercept were not different from unity and zero respectively, indicating that there was no significant systematic error in the method when compared with the direct Fick method. The range of cardiac output measured was from 3.5 to 18 litres/min (Fig 2).

2) Assessment of Random Error

In each subject 12 measurements of cardiac output and stroke volume were obtained, 4 each at different steady states (i.e. rest, exercise at 80W and 130W). The average cardiac output in these three conditions were 6.33 ± 0.22, 10.34 ± 0.33 and 13.06 ± 0.37 l/min respectively. The coefficients of variation of the cardiac output in the four subjects ranged from 2.0% to 3.9% at rest, 1.5% to 3.8% at 80W of exercise and 2.2% to 4.9% at 130W. The overall mean coefficient of variation was 2.97 ± 0.40%. Thus the short term random error of the cardiac output measurements as indicatedd by the coefficient of variation was less than 5%. The corresponding values for the stroke volume ranged from 3.7% to 13.7% at rest, 3.8% to 6.9% at 80W and 2.8% to 5.7% at 130 W of exercise. The coefficient of variation for the heart rate was 1.3% to 6.6% at rest, 1.3% to 6.8% at 80W and 1.0% to 2.9% at 130W.

3) Assessment of Reproducibility

All 6 subjects were able to perform maximal exercise tests one week apart achieving similar end-points in work load. Four achieved workloads of 330W and the other two subjects reached 280W of work. The maximal nature of the exercise was indicated by a plateau in the heart rate response and the oxygen consumption. Reproducibility of performance during the tests was indicated by the highly significant correlations in heart rate and oxygen consumption measured during the two tests (Fig 3 and 4). The average maximum heart rates and oxygen consumption attained during the two tests did not different significanty (mean 175.0 ± 5.6 beat/min, 4.4 ± 0.2 l/min respectively).

The cardiac output measurements showed a highly significant correlation between the two tests (Fig 5). The slope and the intercept of the regression was not different from unity and zero respectively. The stroke volume measurements between the 2 tests showed a correlation coefficient of r=o.84, p<0.001, but the slope of the regression line (0.80) differed significantly from that of the line of identity (Fig 6).

4. Stroke volume-heart rate response to upright exercise

During maximum exercise tests it was found that the stroke volume increased gradually from the value at rest up to a workload of 80W. At workloads in excess of 80W, no increase in stroke volume was observed (Fig 7). The increase in stroke volume occurred at heart rates of 60 to 120 beat/min (Fig 8). Thus, the increase in cardiac output observed at workloads of greater than 80W or at heart rates of greater than 120 beat/min were mediated by increases in the heart rate while the stroke volume was preserved at the maximum value. These findings are comparable to data reported in the literature from several invasive studies (Fig 9 and 10).

Discussion

This study demonstrates the usefulness of Impedance Cardiography for the measurement of stroke volume and cardiac output, at rest and during conventional maximal exercise on a bicycle ergometer. The method is free from any significant systematic error over a range of cardiac outputs from 3.5 to 18 liter/min and has an acceptable short and long term random error. Increases in cardiac output and stroke volume observed in the athletes during maximum exercise were similar to those reported by Astrand et al (22) and also by other investigators (23,24) (Fig 9 and 10).

Methodological Considerations

The variations in electrical impedance to high frequency electrical current has been known since the beginning of the century (1). Later it was observed that these changes were synchronous with the cardiac cycle (6) and have been shown to predominantly reflect changes in the movement of blood ejected from the left ventricle (6-8). A theoretical basis for plethysmography has been described by Geselowitz (25) and Lehr (26). However, the physiological basis for these impedance changes remain constroversial and are probably due to a number of physiological changes that occur both simultaneously and in sequence during the cardiac cycle (11). Kubicek et al (27) using a tetrapolar plethysmograph modified the formula of Nyboer (11) for the measurement of stroke volume. This group also developed the first commercially available impedance cardiograph. A number of factors affect the various components of the Kubicek equation and adjustments have been suggested to improve the accuracy of the measurements. For example, although the left ventricular ejection time could be defined by the dZ/dt wave of the impedance cardiogram (27), a simultaneous phonocardiogram was added to indicate aortic valve closure so as to assist in determining the end of ejection more accurately (28). The measurement of minimum dZ/dt has been the subject of controversy also. Several reports suggested that measurements should be made from the calibration baseline to the peak of the dZ/dt wave form (12,13,27). Others have suggested that the dZ/dt should be measured from the nadir of the initial deflection at the commencement of ejection (15). In the present study, it was found that these two methods of measurement yielded values for cardiac output which were identical at rest and which were found to correlate closely with those obtained simultaneously by the Fick method. However, during exercise, the measurements from the baseline tended to underestimate the stroke volume by as much as 50%. Measurements taken using the initial deflection of the dZ/dt wave just prior to the main upstroke of the dZ/dt wave correlated more closely with that obtained simultaneously from the Fick method (see Fig 11).

Respiration and other body movements also effect the height and the form of the dZ/dt wave. Subjects were requested to stop exercise and to hold their breath at normal end-expiration for the duration of 5 cardiac cycles. This procedure allowed satisfactory recordings to be made at the higher levels of cardiac output achieved during exercise. The break in the exercise induced by this method was too short to produce major changes in hemodynamic variables provided a "steady state" was attained during the exercise (14). Measurements of the heart rate were taken just prior to the end of each workload.

Finally, since a relationship between blood resistivity, hematocrit and body temperature has been demonstrated (29,30), the changes in hematocrit which occur during exercise were taken into account when calculating the cardiac output (30).

Accuracy of the Method

Previous reports have indicated that a discrepancy may exist between the cardiac output measured by impedance cardiography and that measured by other conventional invasive techniques (12,31). In the present investigation a significant correlation with the direct Fick method was achieved by adjusting the factors that affect the Kubicek equation (27) as described above.

The range of cardiac output over which the comparisons were made was between 3.5 and 18 liter/min. This limitation was imposed by the inability of the patients to undertake more strenous exercise during the catheterization. Ethical considerations precluded the catheterization of normal subjects for maximal tests. Although no direct comparisons were made at outputs greater than 18 liter/min, it is of interest to compare the output and stroke volume measurements made during maximal test using impedance cardiography with those reported in the literature from invasive studies at comparable workloads (22-24) (Fig 9 and 10).

The short term random error at rest and during the two stages of steady state exercise were less than 5% and were similar to the results obtained from invasive techniques (32). These random errors were assessed at average cardiac outputs of 6.33 ± 0.22, 10.34 ± 0.33, and 13.06 ± 0.37. No attempt was made to make a formal assessment of the random error at higher cardiac outputs because the protocol demanded that the subject maintain a steady state of exercise for 12-15 minutes. This protocol proved to be difficult to achieve at high workloads.

The physiological response to maximal exercise as indicated by the results of tests performed one week apart by the healthy subjects in this study yielded data which were highly reproducible.There was a significant correlation in heart rate and oxygen consumption at identical maximal work between the two tests. The subjects were chosen on the basis of their well-trained status, and hence their cardiovascular fitness was unlikely to change during the one week interval between tests. In these subjects the measurement of cardiac output on the two occasions showed a highly significant correlation. Variability of stroke volume was greater, especially at rest just prior to starting exercise and during the first stage of exercise. It is likely that this variability is a reflection of the changing physiological status of the subject rather than an intrinsic "error" in the measurement as it was offset by small reciprocal changes in heart rate. No attempt was made to control the time of day of the exercise test, the exercise prior to coming to the exercise laboratory or the diet or fluid intake during the test period.It is suggested that such variations in stroke volume and heart rate could occur as a result of interaction of the sympathetic and parasysmpathetic output to the heart, the state of the preload and the changes in the peripheral resistance at the commencement of exercise (33,34).

Clinical Implications

It is recognized generally that during graded exercise in the erect posture, the stroke volume increases by about 50% as the heart rate increases from 70 beat/min to 110-120 beat/min (22). From this exercise intensity to near maximal exercise stroke volume is maintained while heart rate continues to increase. The findings of the present study are in agreement with the previous findings by invasive methods (22-24). Since increments in stroke volume during modest levels of exercise have been used as a means of evaluating left ventricular function in patients with heart disease, it is suggested that impedance cardiography could prove to be a useful clinical tool, particularly because it is non-invasive. This technique could be done sequentially during graded exercise tests and it is readily repeatable.

In summary, the data in this study suggest that cardiac output, measured by impedance cardiography, at rest and during submaximal and maximal exercise, is accurate and reliable and the results are highly reproducible. The convenience of this non-invasive technique makes it easily and readily adaptable for use during conventional maximum exercise testing in normal subjects.

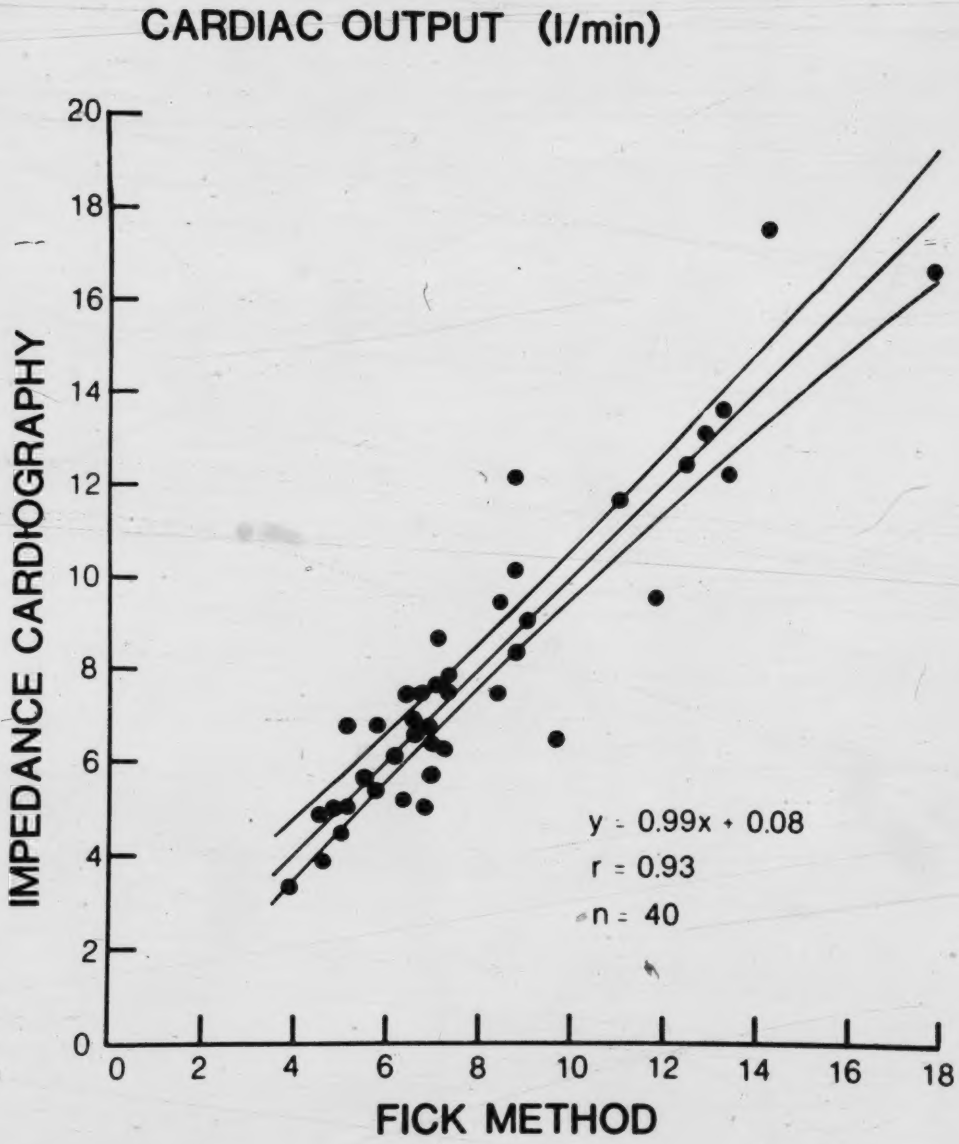
TABLE I

PATIENTS WHO UNDERWENT SIMULTANEOUS MEASUREMENTS OF CARDIAC OUTPUT BY THE FICK METHOD AND IMPEDANCE CARDIOGRAPHY

	n
Males	17
Females	3
No. of measurements made	40
History	
Myocardial infarction (± angina)	7
Angina alone	6
Indications for cardiac catheterization	
Known coronary artery disease	13
Suspected coronary artery disease	5
Evaluation of chest pain murmurs	2
Results of cardiac catheterization	
No. of patients with:	
Significant diseased vessels	17
Aortic stenosis	2
Cardiomyopathy	1
Resting Ejection Fraction	(mean ± SEM)
Total patients (n=20)	61±3%
With Previous infarction (n=7)	52±2%
No previous infarction (n=13)	69±4

Figure 2

SIMULTANEOUS CARDIAC OUTPUTS MEASURED BY IMPEDANCE CARDIOGRAPHY AND THE DIRECT FICK METHOD: Linear regression (± SEM) of simultaneous paired cardiac output measurements by impedance cardiography and direct Fick method. Highly significant correlation was obtained, regression coefficient = 0.93, $p<0.001$, $n=40$). The slope of the regression line and the intercept were not different from unity and zero respectively.



$y = 0.99x + 0.08$

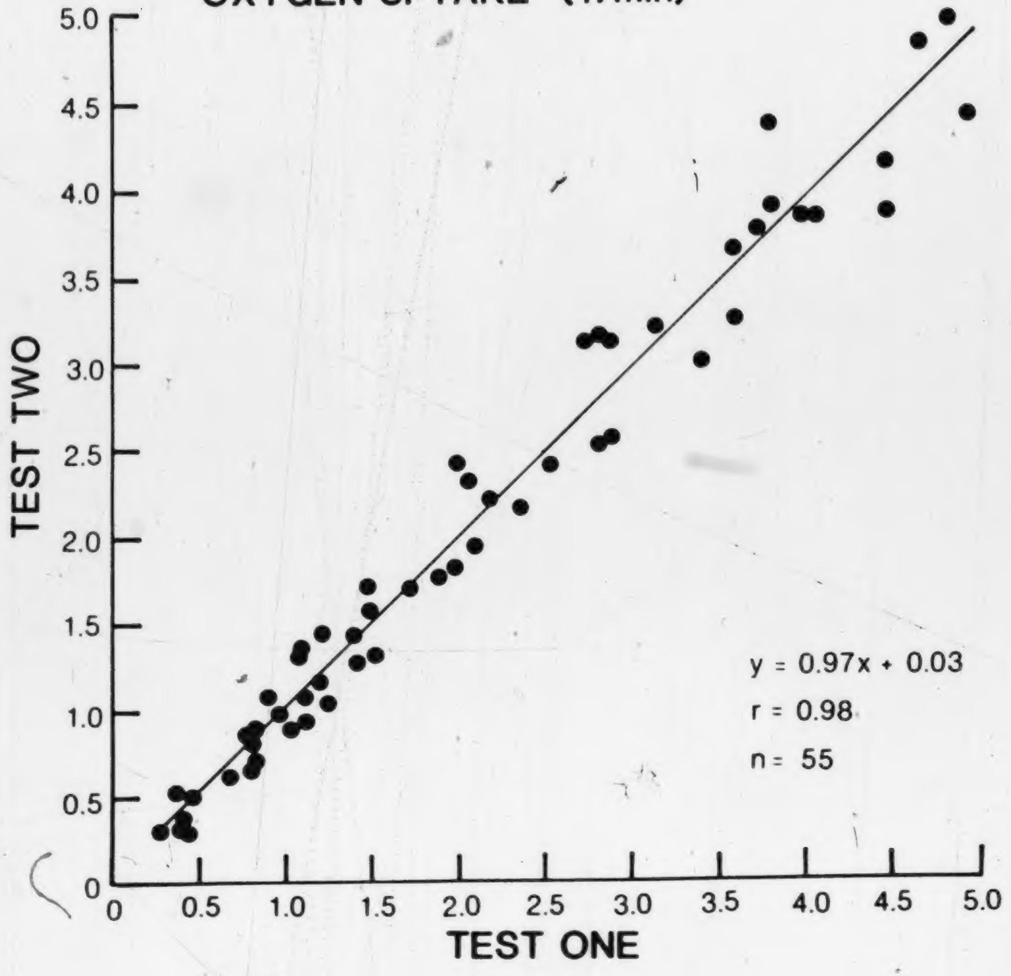
$r = 0.93$

$n = 40$

Figure 3

REPRODUCIBILITY OF OXYGEN UPTAKE DURING MAXIMUM EXERCISE:

Linear regression of oxygen uptake during 2 maximum exercise tests performed one week apart by 6 healthy subjects. Highly significant correlations ($p<0.001$) were obtained comparing paired data obtained during test one (initial test) and test two (repeat test).



OXYGEN UPTAKE (l/min)

Figure 4

REPRODUCIBILITY OF HEART RATE DURING MAXIMUM EXERCISE: Linear regression of heart rate during 2 maximum exercise tests performed one week apart by 6 healthy subjects. Highly significant correlations ($p<0.001$) were obtained comparing paired data obtained during test one (initial test) and test two (repeat test).

9

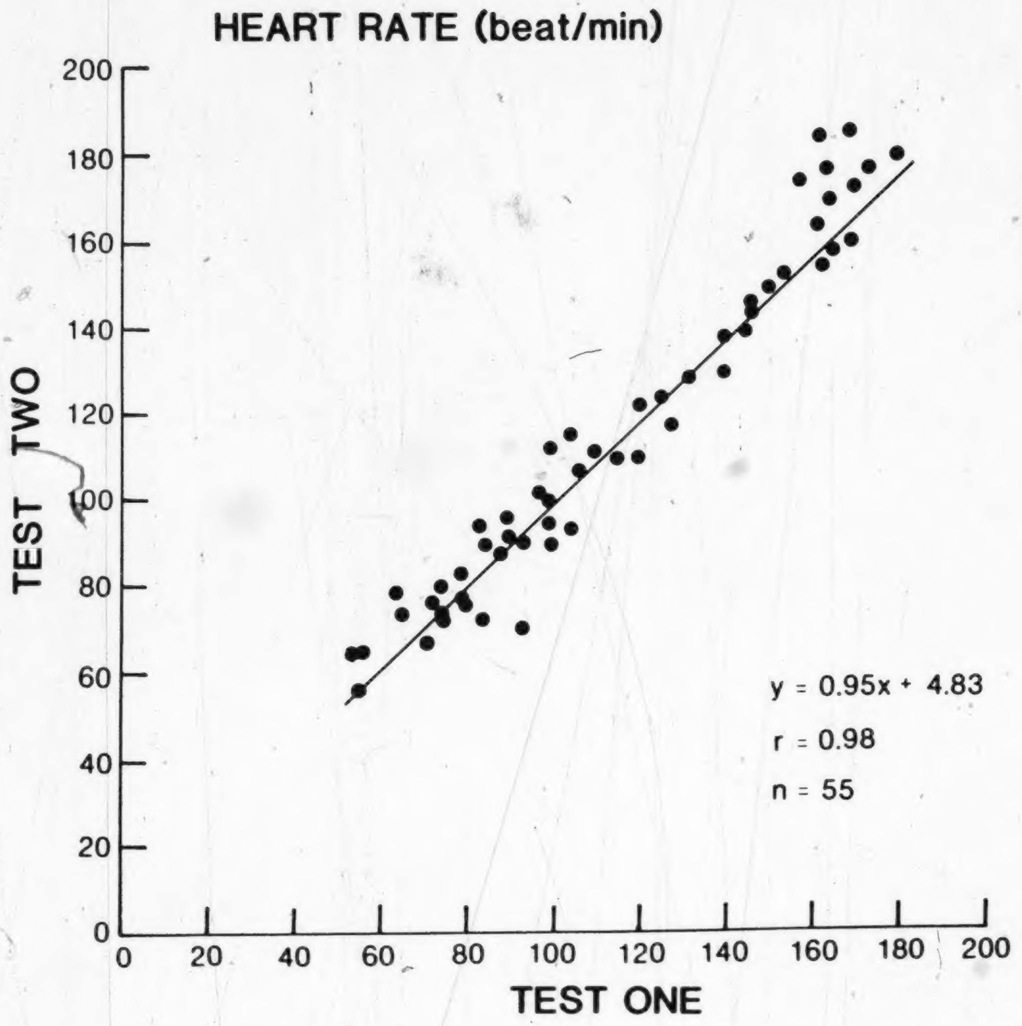

HEART RATE (beat/min)
TEST TWO
200
180
160
140
120
100
80
60
40
20
0
20
40
60
80
100
120
140
160
180
200
TEST ONE
y = 0.95x + 4.83
r = 0.98
n = 55

Figure 5

REPRODUCIBILITY OF CARDIAC OUTPUT DURING MAXIMUM EXERCISE:

Linear regression of cardiac output measured by impedance cardiography during 2 maximum exercise tests performed one week apart by 6 healthy subjects. Highly significant correlations ($p<0.001$) were obtained comparing paired data obtained during test one (initial test) and test two (repeat test).

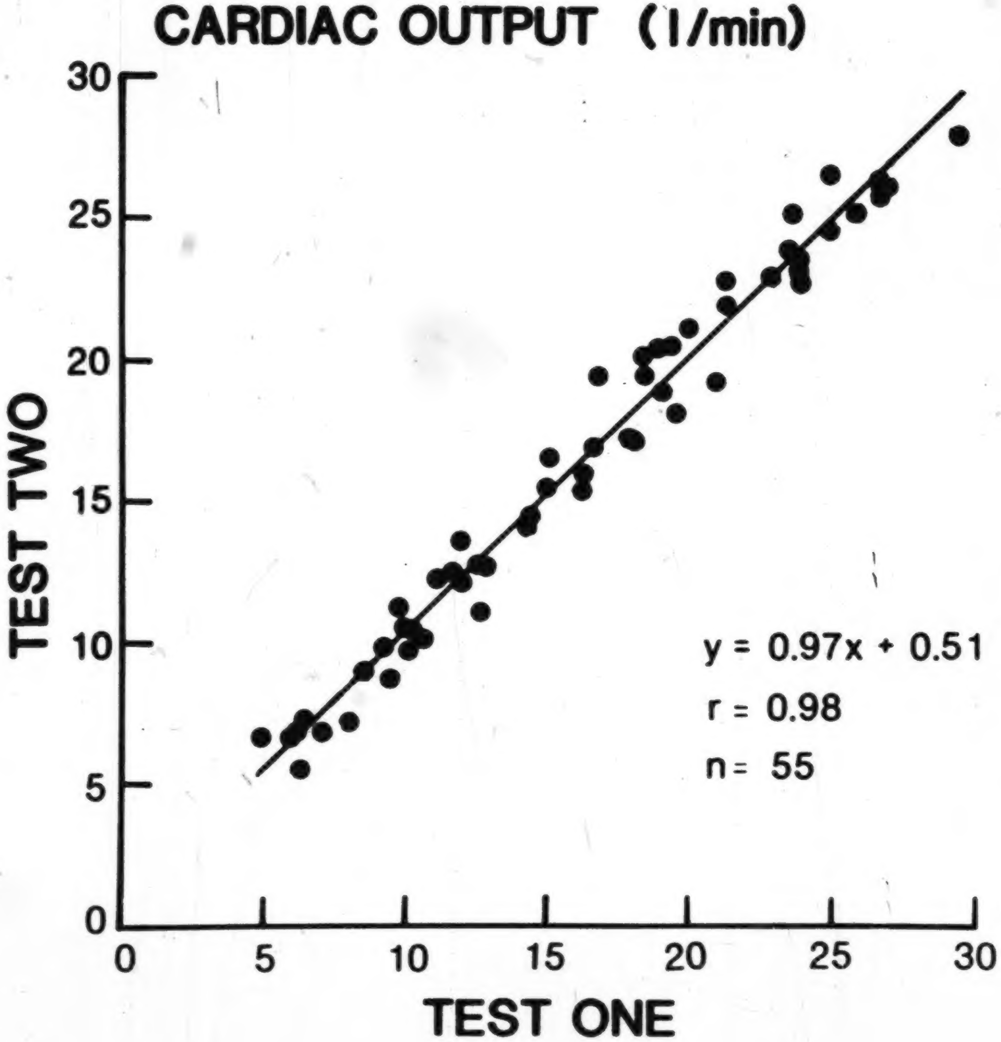

CARDIAC OUTPUT (l/min)
TEST TWO
0
5
10
15
20
25
30
TEST ONE
0
5
10
15
20
25
30
y = 0.97x + 0.51
r = 0.98
n = 55

Figure 6

REPRODUCIBILITY OF STROKE VOLUME DURING MAXIMUM EXERCISE:

Linear regression of stroke volume measured by impedance cardiography during 2 maximum exercise tests performed one week apart by 6 healthy subjects. Highly significant correlations ($p<0.001$) were obtained comparing paired data obtained during test one (initial test) and test two (repeat test).

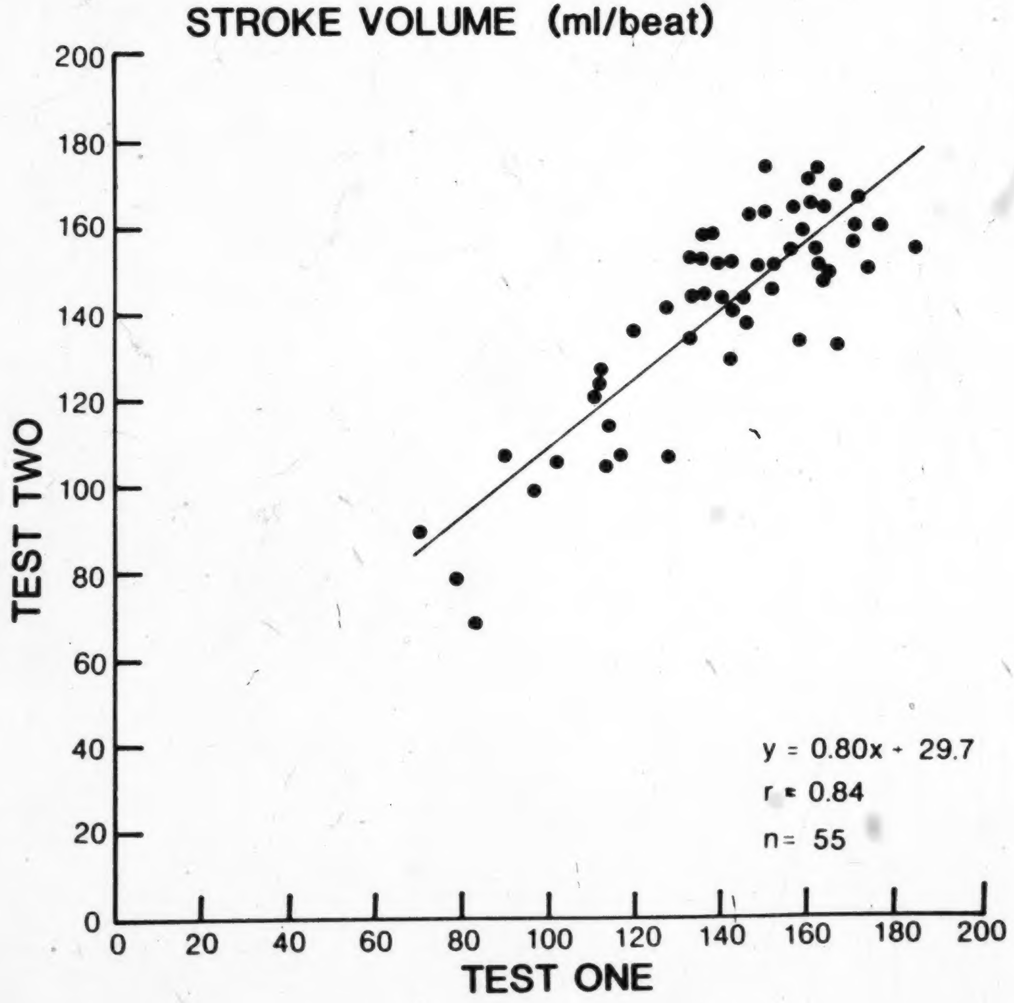

STROKE VOLUME (ml/beat)
TEST TWO
TEST ONE
0
20
40
60
80
100
120
140
160
180
200
y = 0.80x + 29.7
r = 0.84
n = 55

Figure 7

STROKE VOLUME VS WORKLOAD DURING MAXIMUM EXERCISE IN ENDURANCE ATHLETES: Relationship of stroke volume (± SEM) and workload during maximum exercise tests measured in 6 healthy subjects. Maximum stroke volume was achieved at a workload of 80 watts and a heart rate of 120 beats/min.

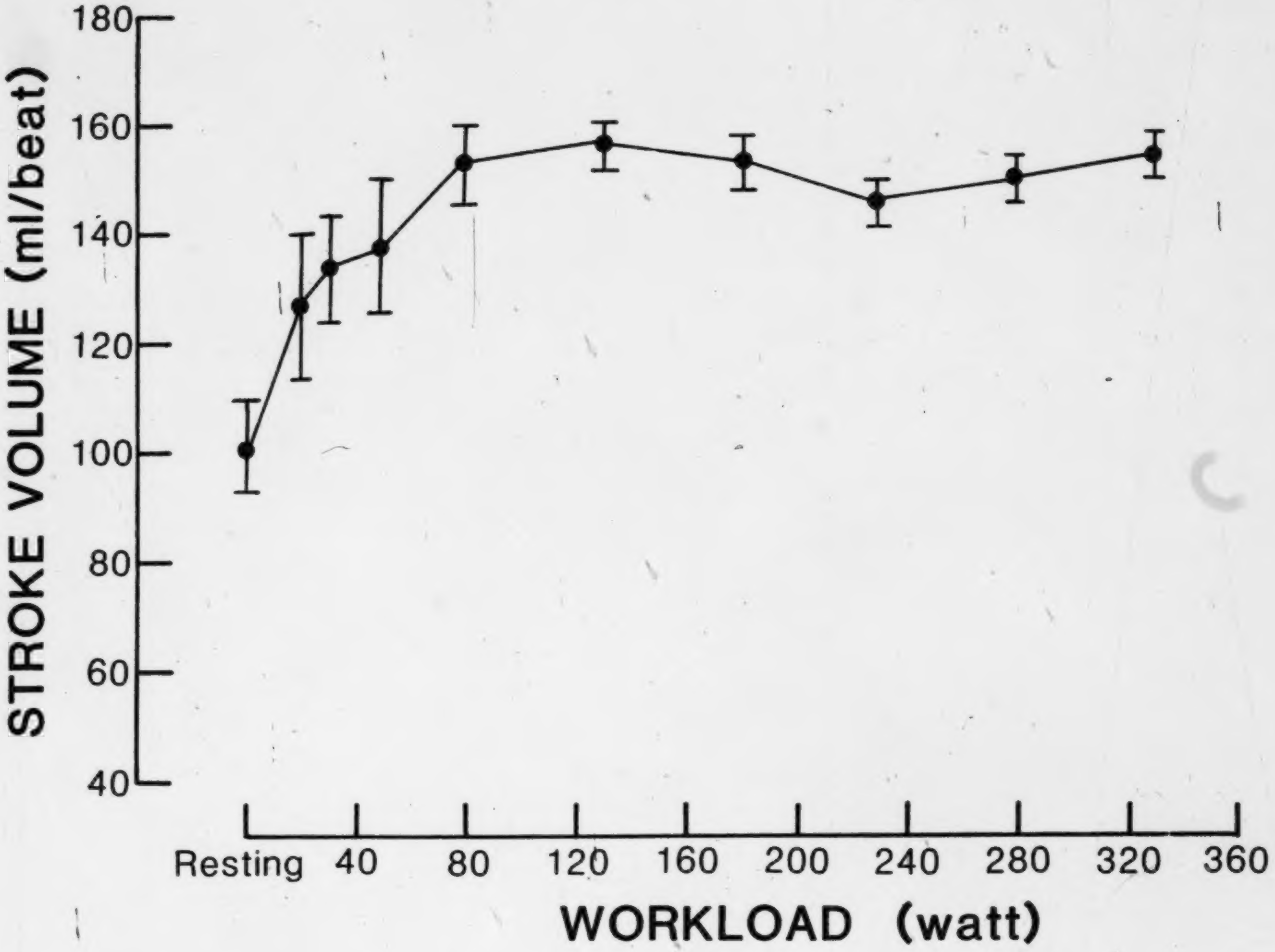

STROKE VOLUME (ml/beat)
180
160
140
120
100
80
60
40
Resting
40
80
120
160
200
240
280
320
360
WORKLOAD (watt)

Figure 8

STROKE VOLUME VS HEART RATE DURING MAXIMUM EXERCISE IN ENDURANCE ATHLETES: Relationship of stroke volume (± SEM) and heart rate during maximum exercise tests measured in 6 healthy subjects. Maximum stroke volume was achieved at a workload of 80 watts and a heart rate of 120 beats/min.

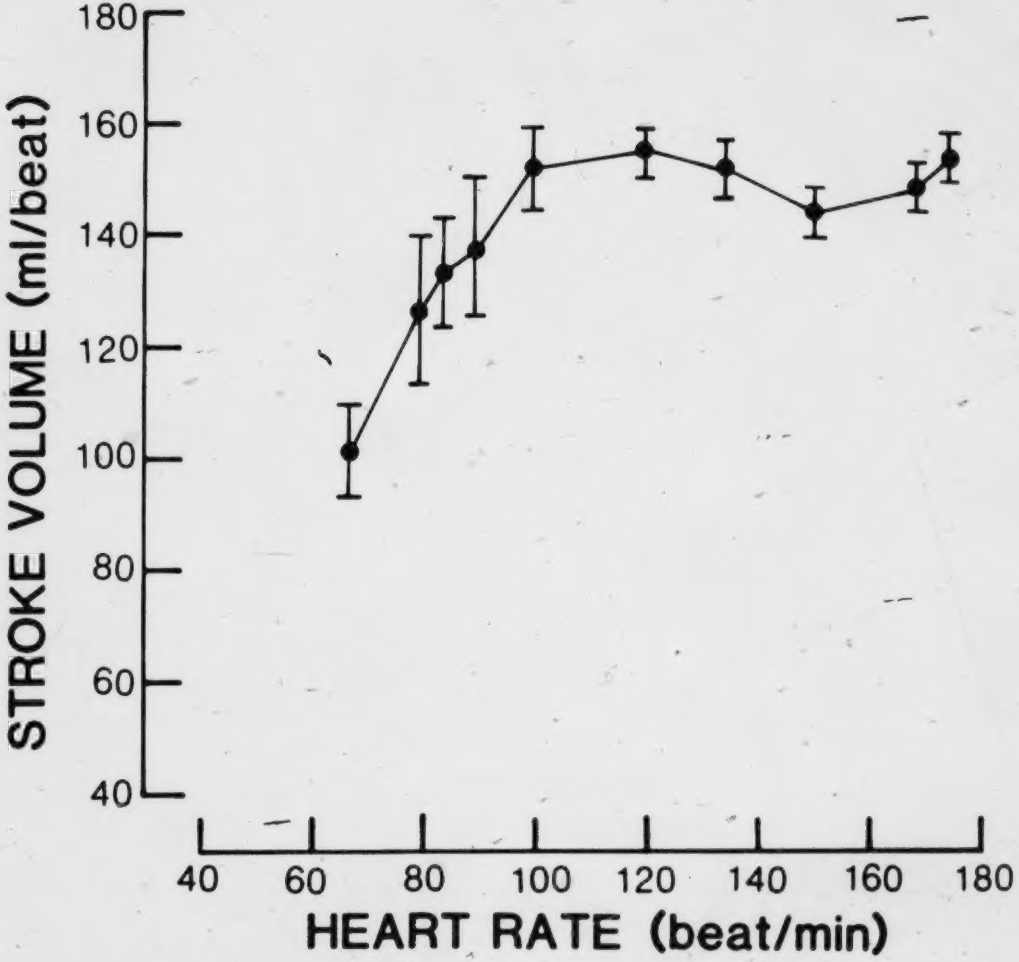

180
160
140
120
100
80
60
40
STROKE VOLUME (ml/beat)
40
60
80
100
120
140
160
180
HEART RATE (beat/min)

Figure 9

CARDIAC OUTPUT MEASURED BY IMPEDANCE CARDIOGRAPHY AND STANDARD INVASIVE METHODS: Relationship between cardiac output and oxygen uptake during maximum exercise tests measured in 6 healthy subjects. Results in this study, (with limits, ± SEM, for both cardiac output and oxygen uptake) were shown together with earlier measurements by standard invasive techniques.

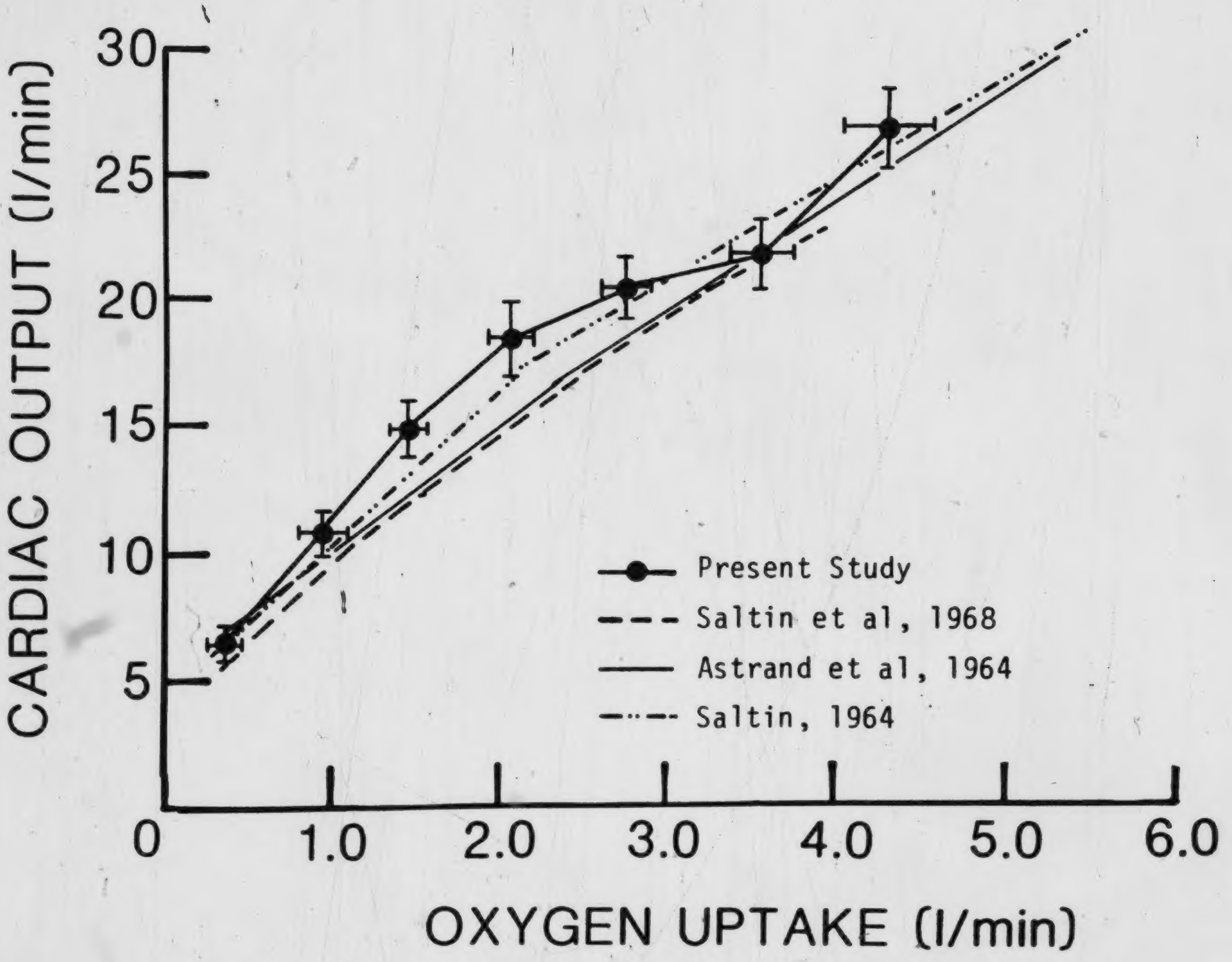
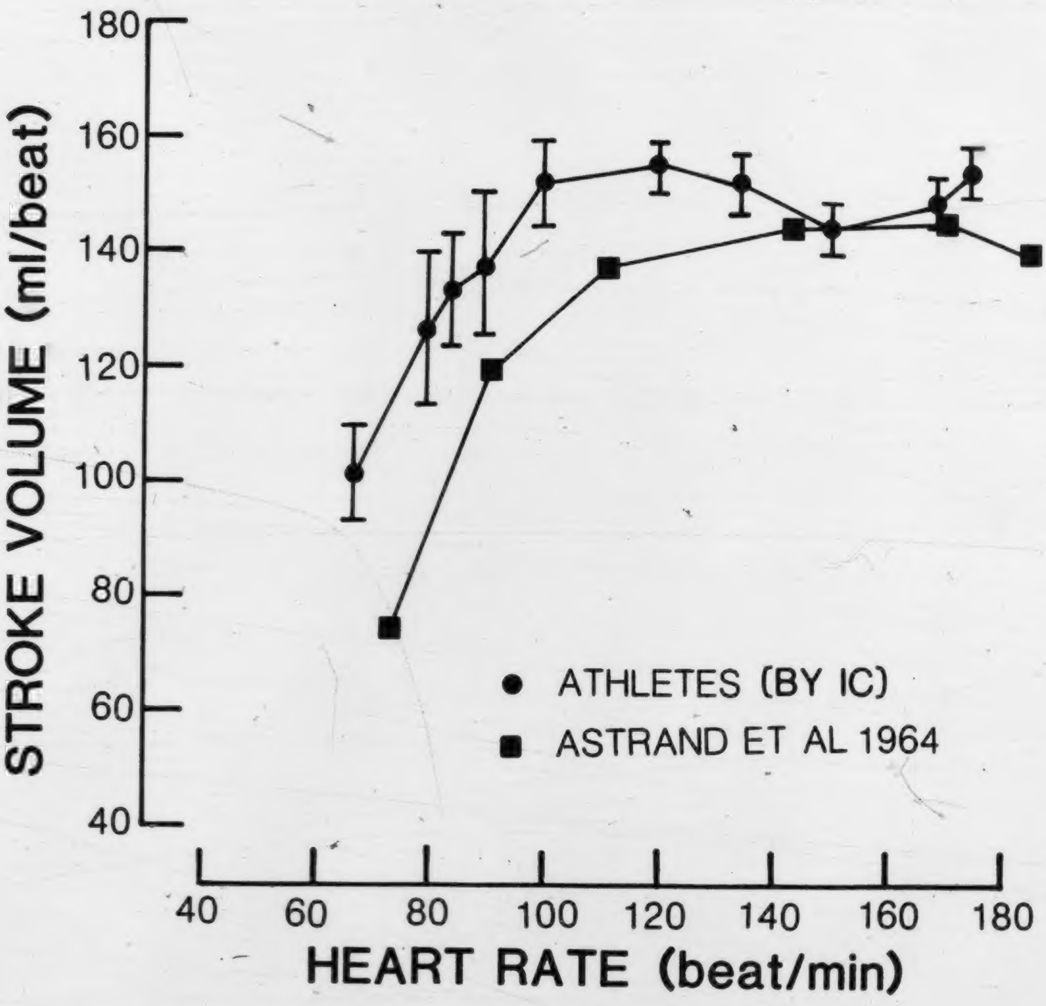

30
25
20
15
10
5
CARDIAC OUTPUT (l/min)
0
1.0
2.0
3.0
4.0
5.0
6.0
OXYGEN UPTAKE (l/min)
Present Study
Saltin et al, 1968
Astrand et al, 1964
Saltin, 1964

Figure 10

STROKE VOLUME MEASURED BY IMPEDANCE CARDIOGRAPHY AND STANDARD INVASIVE METHODS: Relationship between stroke volume and heart rate during maximum exercise tests measured in 6 healthy subjects. Results in this study, (with limits, ± SEM, for stroke volume) were shown together with earlier measurements by standard invasive techniques.


180
160
140
120
100
80
60
40
STROKE VOLUME (ml/beat)
40
60
80
100
120
140
160
180
HEART RATE (beat/min)
● ATHLETES (BY IC)
■ ASTRAND ET AL 1964

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CHAPTER IV

USE OF IMPEDANCE CARDIOGRAPHY IN EVALUATING THE EXERCISE RESPONSE OF PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION[b]

Introduction

In patients with clinical evidence of impaired left ventricular function, measurements of cardiac output, stroke volume, stroke work and ejection fraction at rest are not reliable predictors of the cardiovascular response to exercise (1-4). During submaximal exercise, such patients could exhibit either an appropriate increase in cardiac output and stroke volume or an attenuated response (3,4). Thus, there may be a potential danger in planning regimes of management for patients with poor left ventricular function in the absence of specific information regarding the cardiac output and stroke volume responses to exercise. For instance, a training schedule based upon a target heart rate could place the patient at risk (5,6).

Unfortunately most of the methods of measuring cardiac output are invasive in nature and cannot be adapted readily for use in the out-patient setting. However, impedance cardiography is a non-invasive technique for the measurement of stroke volume and cardiac output. It offers several advantages over the invasive methods of measuring these parameters (7-9). It is a safe, convenient technique which requires little learning by the patient and can be used for making repeated measurements. The cardiac output can be measured reliably and sequentially at rest and during submaximal and maximal exercise in normal subjects (Chapter III). In addition the technique can be adapted easily for use in the outpatient setting.

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[b] A version of this chapter has been published: Hetherington M, Teo KK, Haennel R, Greenwood P, Rossall RE, & Kappagoda T. Use of impedance cardiography in elevating the exercise response of patients with left ventricular dysfunction. European Heart J 1985; 6:1016-1024.

The present investigation was undertaken to determine:

1) whether the stroke volume and cardiac output could be measured by impedance cardiography in patients with coronary artery disease and left ventricular dysfunction.

2) whether the technique is reproducible in patients with left ventricular dysfunction.

3) whether the stroke volume-heart rate response to exercise could be evaluated non-invasively by impedance cardiography in this patient group.

Methods

The two part of this study were undertaken in a group of patients presenting to the Cardiology Service at the University of Alberta Hospital, Edmonton. In the first part of the study, the long term reproducibility of the cardiac output and stroke volume measurements determined by impedance cardiography was examined during two graded exercise tests done one week apart. Secondly, the exercise response was examined in a group of patients with known left ventricular dysfunction.

1) Long term reproducibility

The reproducibility of the technique was determined by measuring the stroke volume and cardiac output response to submaximal exercise in 5 patients with left ventricular dysfunction. These patients were randomly selected from the 15 patients who participated in the second part of this study (see Table II). Each underwent a submaximal bicycle exercise test on 2 occasions one week apart. The patients came to the exercise laboratory at the same time of day, 7 days apart, being careful to have taken their medication at the same time prior to each test. Stroke volume and cardiac output was measured at rest and at each 3 minute stage of exercise up to a 'symptom-limited' level of exercise (see "General Methods").

2) Exercise response in patients with left ventricular dysfunction

Fifteen patients, who had sustained a major myocardial infarction 6 to 12 months previously were investigated. Symptomatically, this group of patients were in Functional Class II or III of the New York Heart Association Classification (10). All exhibited evidence of immediate post infarction failure. Resting left ventricular ejection fractions (LVEF) were measured by radionuclide ventriculography and ranged from 17% to 65% at the time of the study. Medication was not discontinued and included digitalis in 5, beta-blockers in 3, diuretics in 5 and vasodilators in 4 patients. The clinical information from this group is given in Table II. At the time of the study none of the patients had clinical evidence of heart failure.

All patients underwent an exercise stress test using the protocol as outlined previously in 'General Methods'.

Statistical Methods

1) Reproducibility was assessed by comparing the data from the two tests done one week apart using a least square regression analysis (11).

2) Patients were classified into 2 groups according to the profile of the stroke volume response to increasing workloads and heart rate. Significant differences in the group responses at individual workloads was assessed by the Wilcoxon rank sum test for two independent samples (11). Minimum level of significance for all comparisons was taken to be $p<0.05$.

Results

Background Clinical Data on Patients Studied

The 5 patients studied in part 1 all had a history of myocardial infarction. The resting ejection fractions of this group ranged from 22-40% as determined by radionuclide ventriculography (see Table II for details).

The 15 patients studied in part 2 of the study also had a history of myocardial infarction and had clinical evidence of acute left ventricular failure during the acute phase of the illness. The clinical details for these patients are as shown in Table II.

Reproducibility

A significant correlation was obtained between the cardiac output and stroke volume measured one week apart in each of 5 patients. Regression analysis of the two sets of data yielded regression coefficients of 0.94 ($p<0.001$) and 0.93 ($p<0.001$) for cardiac output and stroke volume respectively (Fig 11 and 12 respectively).

Exercise Response in Patients

The stroke volume data from the fifteen patients were first examined to determine whether or not there were any obvious differences in the profile of the stroke volume and cardiac output responses to graded upright exercise. In 7 patients the stroke volume and cardiac output was found to increase in the normal fashion with successive increases in work and heart rate (Group A) (Fig 13 and 14 respectively). In the remaining 8 patients, the stroke volume failed to increase or dropped at moderate workloads and at heart rates of greater than 100 beat/min (Fig 13). The cardiac output in this latter group failed to rise in appropriate increments or to sustain an increase during graded exercise (Group B) (Fig 14). When the data was analysed after the initial separation (i.e. on the basis of the stroke volume profiles to increasing heart rates), the patients in Group A showed a significantly larger cardiac output ($p<0.05$) at 70 W and a significantly larger stroke volume ($p<0.05$) at 30, 50 and 70 W than did patients in Group B.

In addition, heart rates were higher in Group B than in Group A at workloads of 50, 70 and 90W (Fig 15). The mean arterial pressure was also higher in Group B than in Group A at 70 and 90W (Fig 16). The

Norris Index and the resting ejection fraction was not different between the 2 groups (see Table II).

Of the 7 patients in Group A, the test was terminated due to chest pain in one and fatigue in 7 patients. In Group B (n=8), the test was terminated due to a fall in blood pressure response in 3 and fatigue in 5.

Discussion

This study was undertaken to establish the feasibility of using impedance cardiography to measure the cardiac output responses to exercise in patients with clinical manifestations of left ventricular dysfunction. Invasive studies in such patients have revealed a variety of changes in stroke volume, left ventricular filling pressure, cardiac output, mean systolic pressure and systemic vascular resistance (3,4). These reported studies have indicated that the direction of change in these parameters could not be predicted with certainty from the measurements obtained at rest. Under these circumstances it would be of considerable value to have a non-invasive method of measuring stroke volume and cardiac output during exercise which could be adapted easily for use in the outpatient setting.

The findings of the present study demonstrate that impedance cardiography was reproducibile over one week and could be used to measure stroke volume and cardiac output response during graded exercise in patients with left ventricular dysfunction. As demonstrated in the previous series of experiments, no systematic error could be demonstrated with the technique when compared with the direct Fick method in patients undergoing routine diagnostic cardiac catheterization.

The data obtained in the second part of this study suggest that conventional end-points of exercise testing, such as angina, attainment of 85% of predicted maximum heart rate, abnormal blood pressure response or excessive dyspnea or fatigue did not consistently indicate a reason for terminating the test in the patients who exhibited an abnormal stroke volume and cardiac output "profile" during exercise. Only one patient developed ischemic changes during the exercise test and 3 had an attenuated blood pressure response; all patients experienced fatigue and mild dyspnea. However, patients in Group A were able to increase both stroke volume and cardiac output with increasing workloads while patients in Group B were unable to increase stroke volume in the normal fashion. Although they demonstrated an exaggerated heart rate response, their cardiac outputs remained attenuated during exercise (Fig.13).

Impedance cardiography appears to be a reliable method for evaluating stroke volume, heart rate and cardiac output in patients with known left ventricular dysfunction at rest. In addition, the findings reported here may be of practical importance in the long term management of patients when using vasodilators or determining exercise prescriptions. In patients who exhibit left ventricular dysfunction during exercise, it may be inappropriate to encourage some patients (i.e. those in Group B) to attempt levels of exercise which result in a blunting of the cardiac output due to a failure to increase stroke volume or to drop stroke volume during exercise.

TABLE II

CHARACTERISTICS OF INDIVIDUAL PATIENTS

	SEX	AGE(YR)	MI SITE	CK(IU/L)[1]	NOR.IND[3]	EF(%)[4]	WL[5]	DRUG[6]
Group A								
1	M	48	AWMI	2011	2.51	28	110	D
2	F	61	SEND	922	2.94	65	50	-
3*	M	53	AWMI	1625	7.06	22	90	D
4*	M	48	AWMI	4000	0.98	29	70	B
5	M	58	AWMI	2853	5.19	17	50	D
6	M	36	AWMI	369	5.93	38	70	DNPIDi
7	F	60	IWMI	236	2.94	53	70	Di
Mean ± SEM		52.0±3.3		1717±517	3.9±0.8	36.0±6.6%	72.9±8.1	
Group B								
1*	M	53	AWMI	1177	7.06	37	90	D
2	M	75	AWMI	3065	7.15	25	50	Di
3	M	54	AWMI	354	6.99	32	70	-
4	F	70	AWMI	1591	3.95	50	90	BIDi
5*	M	51	AWMI	118	3.46	40	90	N
6*	M	64	AWMI	(-)[1]	2.94	38	70	
7	M	45	AWMI	3895	4.21	55	70	BI
8	M	38	IWMI	2040	2.51	43	70	Di
Mean ± SEM		56.3±4.4		1749±519	4.8±0.7	40.0±3.4	75±5	

AWMI: Anterior Wall Myocardial Infarction
IWMI: Inferior Wall Myocardial Infarction
SEND: Subendocardial Infarction
1 CK: Highest creatine phosphokinase level measured in Coronary Care Unit
2 Data Not Available
3 NOR.IND: The Norris Prognostic Index was compiled from the following factors: age, previous history of infarction, radiological evidence of pulmonary congestion and radiological evidence of cardiomegaly (12).
4 EF: Ejection fraction at rest was measured in these patients using a conventional radionuclide ventriculography technique (13,14).
5 WL: Maximum Workload attained
6 Drug: D = digoxin; B = β blocker, I = isordil, P = prazosin, Di = diuretics, N = nifedipine
* Underwent reproducibility studies (2 exercise tests 1 week apart).

Figure 11

REPRODUCIBILITY OF CARDIAC OUTPUT IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Comparison of paired cardiac output (l/min) at rest and during symptom-limited maximum graded bicycle ergometer exercise, measured by impedance cardiography, one week apart by impedance cardiography in five cardiac patients with left ventricular dysfunction. A highly significant linear correlation for cardiac output (r=94, p<0.001) was obtained.

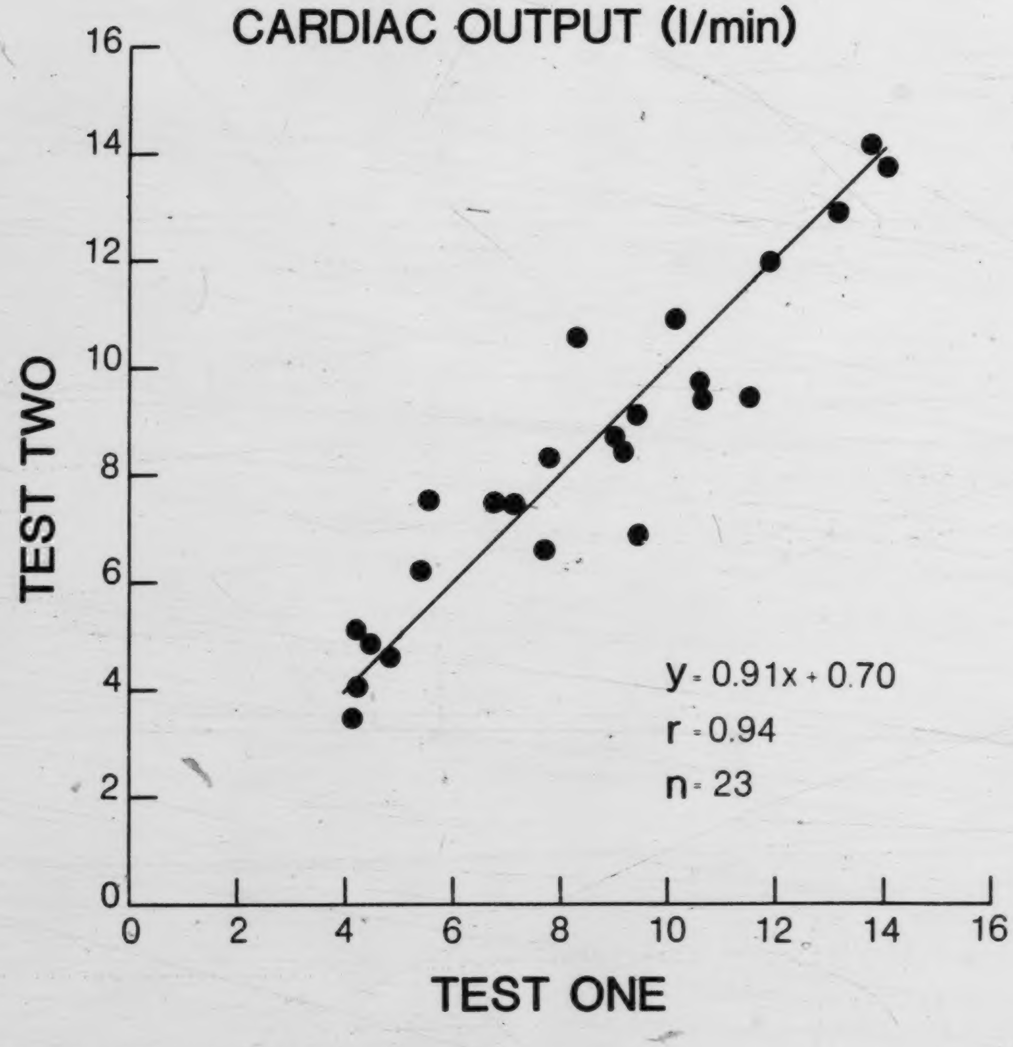

CARDIAC OUTPUT (l/min)
TEST TWO
TEST ONE
0
2
4
6
8
10
12
14
16
0
2
4
6
8
10
12
14
16
y = 0.91x + 0.70
r = 0.94
n = 23

Figure 12

REPRODUCIBILITY OF STROKE VOLUME IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Comparison of paired stroke volume (ml/load) at rest and during symptom-limited maximum graded bicycle ergometer exercise, measured by impedance cardiography, one week apart by impedance cardiography in five cardiac patients with left ventricular dysfunction. A highly significant linear correlation for stroke volume ($r=0.93$, $p<0.001$) was obtained.

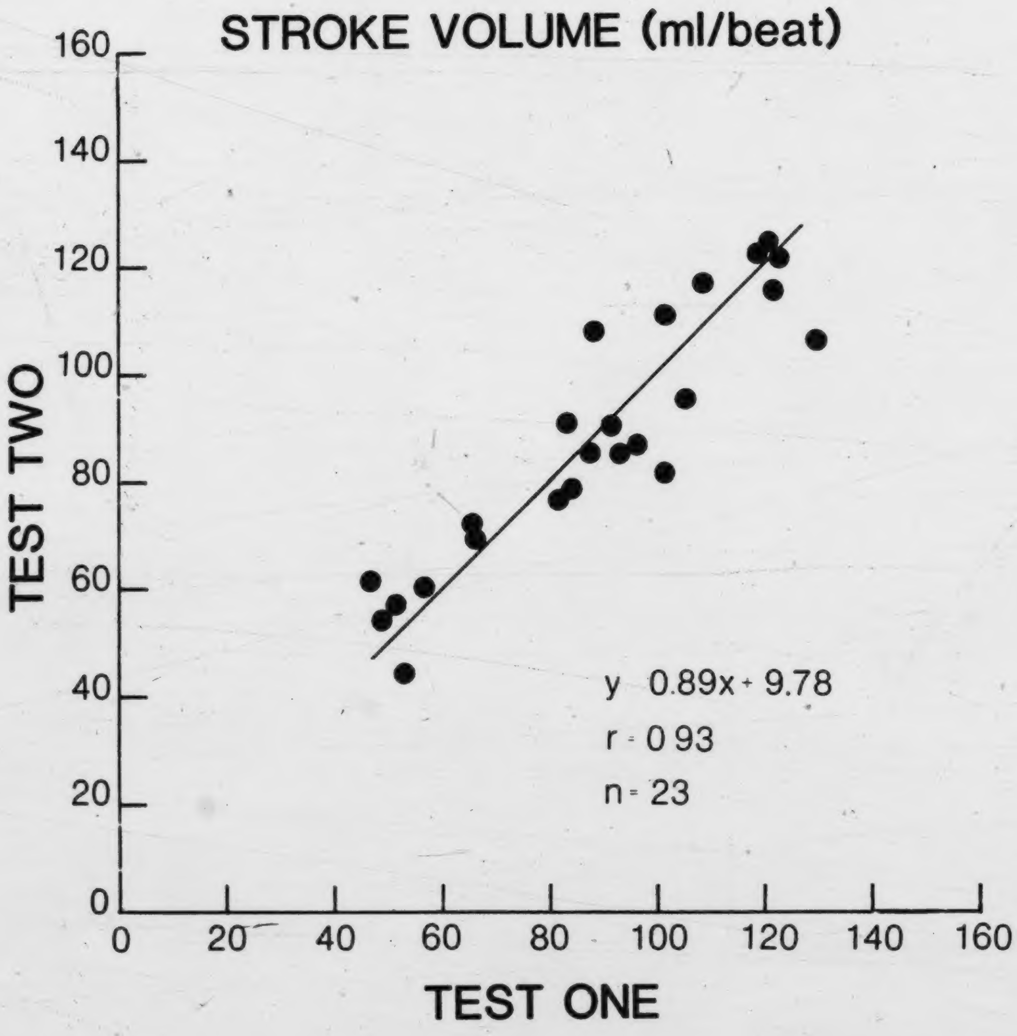

STROKE VOLUME (ml/beat)
TEST TWO
TEST ONE
0
20
40
60
80
100
120
140
160
y = 0.89x + 9.78
r = 0.93
n = 23

Figure 13

STROKE VOLUME-HEART RATE RESPONSE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Changes in stroke volume (ml/beat) and heart rate (beat/min) during graded upright exercise on a bicycle ergometer. The patients with left ventricular dysfunction exhibited two patterns of stroke volume response (Group A, n=7; Group B, n=8). The values shown are mean ± SEM and each point is derived from the coordinator for the workloads defined in the protocol.

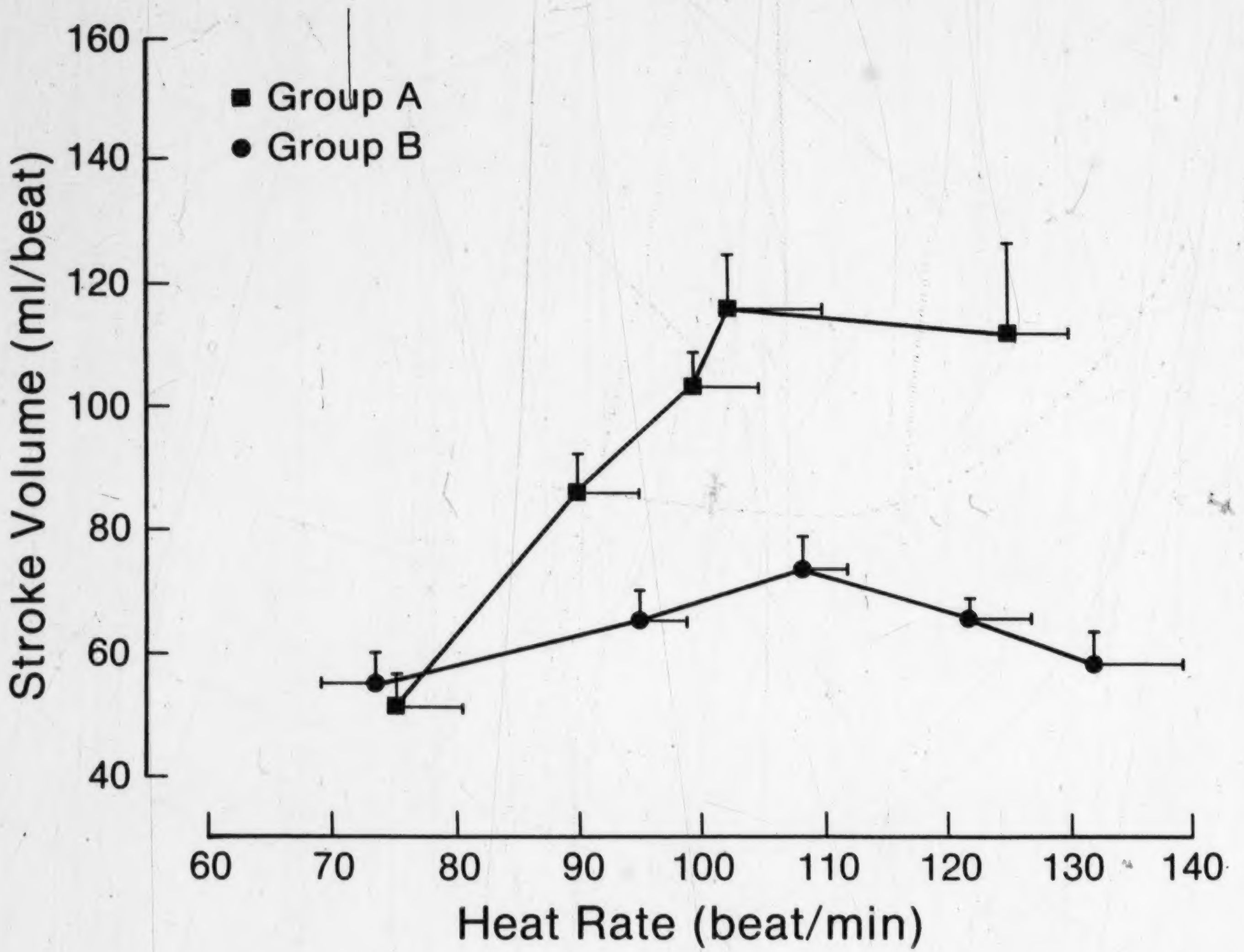

Group A
Group B
Stroke Volume (ml/beat)
160
140
120
100
80
60
40
60
70
80
90
100
110
120
130
140
Heat Rate (beat/min)

Figure 14

CARDIAC OUTPUT DURING EXERCISE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Cardiac output (litre/min) during upright bicycle ergometer exercise by patients with left ventricular dysfunction who are classified into Group A (n=7) and Group B (n=8). Values shown are mean ± SEM. A significantly higher cardiac output was found in Group A compared to Group B, as indicated by (*). Only 3 patients in each group completed the 90 Watt load.

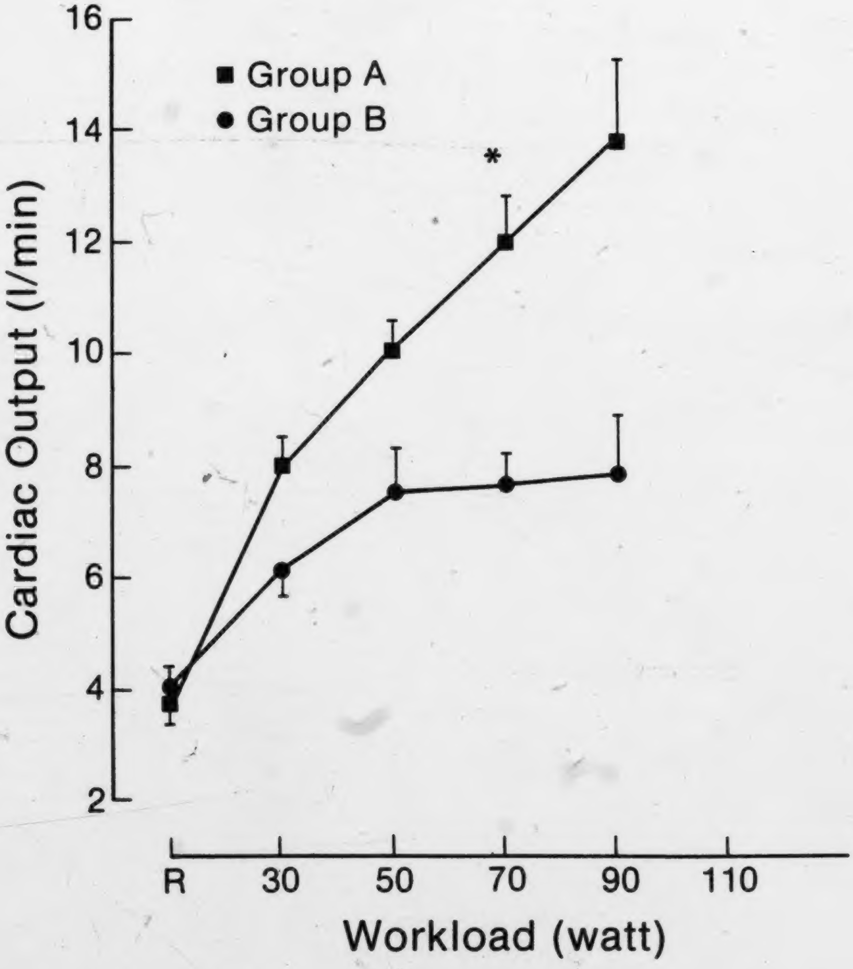

16
14
12
10
8
6
4
2
Cardiac Output (l/min)
■ Group A
● Group B
*
R
30
50
70
90
110
Workload (watt)

Figure 15

HEART RATE DURING EXERCISE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Heart rate (beat/min) during upright bicycle ergometer exercise patients with left ventricular dysfunction who are classified into Group A (n=7) and Group B (n=8). Values shown are mean ± SEM. No significant differences in heart rate were found between the 2 groups. Only 3 patients in each group completed the 90 Watt load.

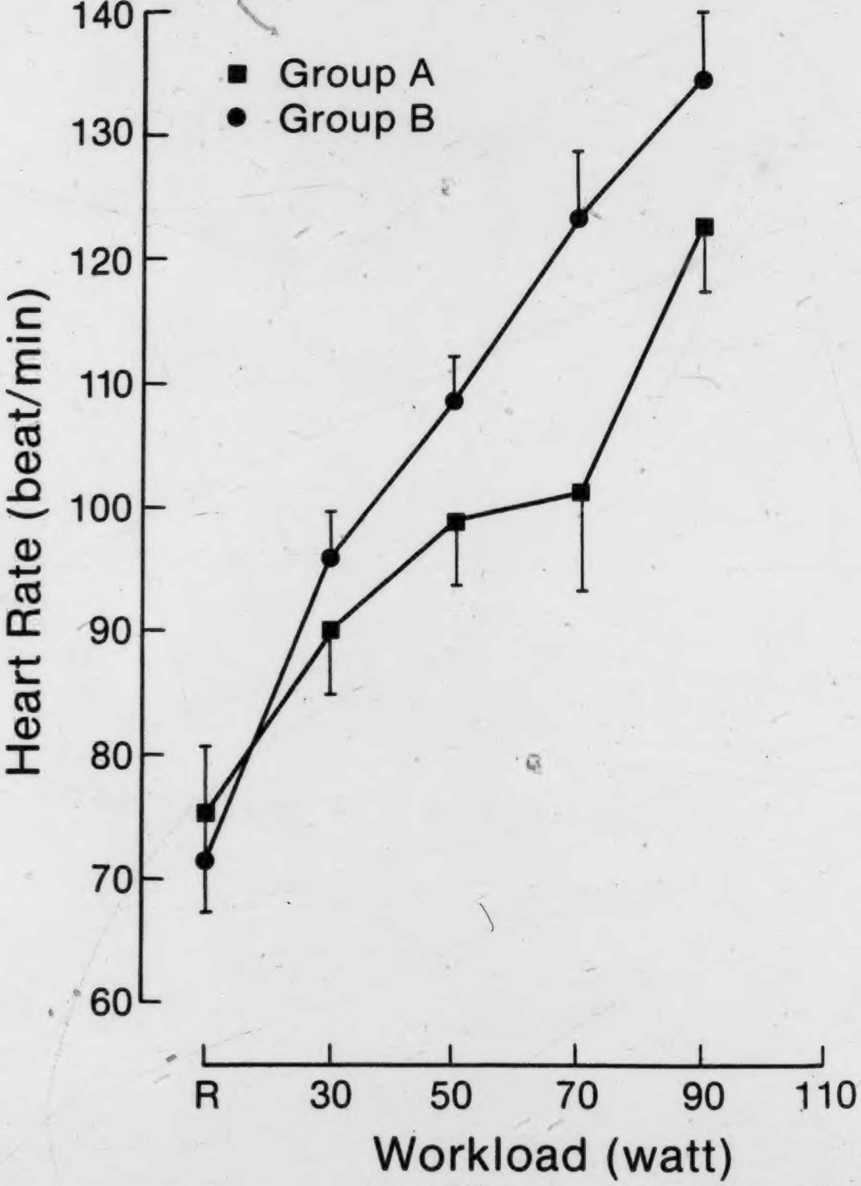
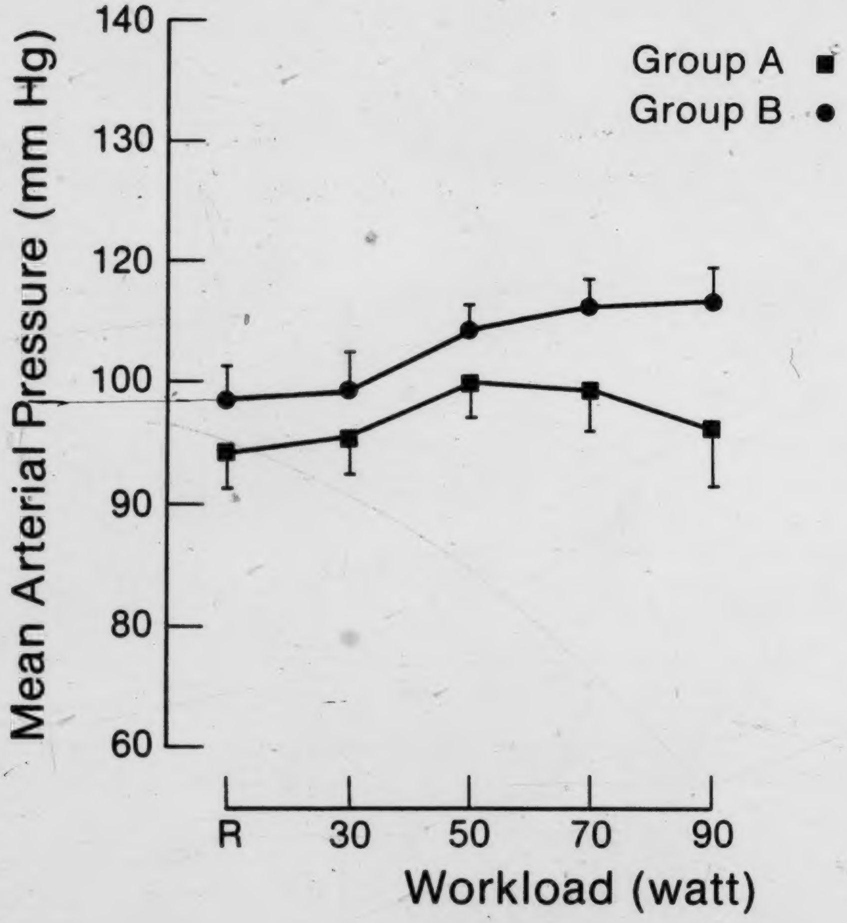

140
130
120
110
100
90
80
70
60
■ Group A
● Group B
Heart Rate (beat/min)
R
30
50
70
90
110
Workload (watt)

Figure 16

MEAN ARTERIAL PRESSURE DURING EXERCISE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: Mean arterial pressure (mm Hg) during upright bicycle ergometer exercise by patients with left ventricular dysfunction who are classified into Group A (n=7) and Group B (n=8). Values shown are mean ± SEM. No significant differences in mean arterial pressure were found between the 2 groups. Only 3 patients in each group completed the 90 Watt load.


Mean Arterial Pressure (mm Hg)
140
130
120
100
90
80
60
Group A ■
Group B ●
R
30
50
70
90
Workload (watt)

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CHAPTER V

RESPONSE TO UPRIGHT EXERCISE AFTER MYOCARDIAL INFARCTION[c]

Introduction

The responses of the heart in normal subjects undergoing graded exercise in the upright posture are well known (1). The heart rate increases in an almost linear manner until the maximum oxygen consumption is approached. The stroke volume increases from the resting value during the initial phase of exercise and reaches a maximum at heart rates between 110-120 beat/min. The intensity of exercise at this stage corresponds to 30-40% of the maximum oxygen consumption. When the intensity of exercise is increased beyond this value, the stroke volume remains steady and the heart rate alone continues to increase. At maximum exercise the heart rate fails to increase further and the stroke volume may diminish 3-5% (1).

Previous results from this laboratory (Chapter IV) suggested that patients with left ventricular dysfunction exhibited either a normal or abnormal stroke volume-heart rate relationship (i.e. stroke volume increased with mild exercise then fell with higher workloads or failed to increase with the onset of exercise). This relationship between the stroke volume and the heart rate in patients recovering from a myocardial infarction is not well understood, due mainly to the difficulties in obtaining sequential measurements of stroke volume when such patients undertake exercise in the upright posture. However, the technique of impedance cardiography being both non-invasive and adaptable for use in the outpatient setting is suited for this purpose (2). The investigation described in this paper was undertaken to determine the relationship between stroke volume and heart rate in post myocardial infarction patients undergoing exercise in the upright posture.

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[c] A version of this chapter has been submitted for publication: Hetherington M, Teo KK, Haennel RG, Kappagoda T, & Rossall RE. Response to upright exercise after myocardial infarction. Cardiovascular Research, 1986.

Methods

Subjects

The study group consisted of a series of patients who had suffered a myocardial infarction 8-10 weeks prior to the investigation. The patients were enrolled in the Cardiac Rehabilitation Program at the University of Alberta Hospital, Edmonton, Canada, and were examined at this time as part of the routine follow-up available at this institution. The study was limited to patients under 70 years of age.

Medication was not manipulated prior to the test. Patients who were receiving beta-blocking agents were not included in the analysis nor were those unable to complete three workloads during the exercise test. Apart from these exclusion criteria, the group examined consisted of consecutive patients.

A small group of normal sedentary individuals receiving no medications were also studied to generate "normal" data for comparison.

Protocol for Exercise Tests

i) Patients

The participants came to the exercise laboratory in a fasting state. All were familar with the testing procedure as they had undergone a low level exercise test prior to discharge from the hospital, 10-14 days following the acute infarct. This low level stress test was not done if the patient showed signs of left ventricular failure, had a systolic blood pressure of less than 95 mm Hg, experienced significant arrhythmias or had unstable angina and were excluded from the present investigation (3).

The exercise test and the end-points of the stress test were the same as outlined in the "General Methods".

ii) Normal Subjects

The normal subjects also exercised in the upright position on a bicycle ergometer. The load was set 20W and increased to 30W, 50W and 80W every three minutes. The load was then increased by 50W increments until the subject experienced exhaustion and a plateau in oxygen consumption and heart rate was apparent with further increases in work. Oxygen consumption was measured at rest and during exercise in the normal controls by a continuous flow technique (4).

Stroke Volume Measurement

Stroke volume, heart rate and cardiac output were measured by impedance cardiography using the procedure for both the post infarction patients and the normal subjects as outlined in the "General Methods".

Mean arterial pressure was determined at rest and during exercise by adding 1/3 of the pulse pressure to the diastolic blood pressure which was measured by sphygmomanometer. Systemic vascular resistance was calculated by dividing the mean arterial pressure by the cardiac output.

Echocardiography

Two dimensional and M-mode echocardiography recordings were made on the same day as the exercise test using a Diasonics Cardio-Vue 3400R Phased Array ultrasonograph. The ventricles were assessed for asynergy by two dimensional echocardiography using parasternal long axis and tomographic short axis views. Apical 4 and 2 chamber views were also recorded.

M-mode recordings were made from the parasternal long axis and parasternal short axis views at the level of the chordae tendinae to demonstrate left ventricular wall motion, aortic and mitral valve motion, and chamber sizes.

Left Ventricular angiography and coronary arteriography

Conventional left ventricular angiography and coronary arteriographic studies were done during the first 12 months following the acute infarction. Coronary arteriography was performed in multiple projections by the Judkins method (5).

The coronary arteries were graded using the scoring system, based on severity of the disease, adopted by the American Heart Association (6). In addition, both left ventricular end-diastolic volume index and end-systolic volume index were calculated using the area-length method (7).

The left ventricular ejection fraction was measured at rest by radionuclide ventriculography (8,9) on the same day as the exercise test.

Statistical Analysis

All group data was expressed as the mean ±standard error of the mean. A one way analysis of variance was done to estimate the difference between groups (10) for the parameters examined (i.e. stroke volume, heart rate, cardiac output, mean arterial pressure and systemic vascular resistance). When the F ratio demonstrated significance at the 0.05 level, the Fischer Least Significant Difference test was used to determine where these differences lay.

Results

Seventy-three patients were studied over a nine month period 8-10 weeks after recovery from a myocardial infarction. During this time, 172 patients were admitted to this institution with a diagnosis of acute myocardial infarction. Ninety-nine of these patients did not return for the follow-up test (see Figure 17 for details). Patients (n=27) who were receiving beta-blocking agents at the time of the test were excluded from this analysis, as were 7 patients who were unable to complete more than two stages of exercise.

The thirty-nine remaining patients (35 males and 4 females) were studied 8-10 weeks after recovery from their infarctions. The average age of these patients was 54.2 ± 1.7 years. The mean resting left ventricular ejection fraction in this group of patients was 41.9 ± 2.3%. Other relevant clinical details of these patients are given in Table III. Nine normal subjects with a mean age of 49.8 ± 0.9 years were also studied.

Exercise Response in Normal Subjects

The nine age matched control subjects exhibited a mean stroke volume of 74.3 ± 6.4 ml/beat and a heart rate of 79.3 ± 4.8 beat/min while sitting quietly on the bicycle ergometer in the erect posture. The corresponding mean cardiac output was 5.7 ± 0.3 l/min. During exercise, the stroke volume increased to a maximum value of 107.7 ± 5.6 ml/beat at a heart rate between 110 and 120 beat/min. The stroke volume then remained unchanged until maximum heart rates and workloads were approached at which time the stroke volume decreased by 2.3 ± 0.5% in 7 of the 9 individuals. The cardiac output and the heart rate continued to increase until maximum values of 17.2 ± 0.7 l/min and 160.0 ± 3.1 beat/min were reached respectively. The work load completed was 218 ± 11W. These observations are comparable to those reported by Astrand for middle aged sedentary individuals (11).

Exercise Response in Cardiac Patients

The thirty-nine post infarction patients had a mean heart rate and stroke volume of 71.1 ± 1.8 beat/min and 58.8 ± 2.5 ml/beat respectively while sitting quietly on the bicycle ergometer in the upright position.

In these patients the maximum work load achieved was 96.1 ± 4.0W and the symptom-limited maximum heart rate was 128.4 ± 2.8 beats/min.

The stroke volume responses during exercise exhibited three distinct patterns in these patients. Fourteen patients (Group A) exhibited a 'normal' response. The stroke volume increased during the initial phase of exercise (i.e. at heart rates between 70 and 110 beat/min) and remained at this maximum value for the duration of the exercise.

Twenty-five patients exhibited an abnormal stroke volume response during exercise. Thirteen of them (Group B) increased their stroke volumes during the initial workloads but with continued exercise which demanded heart rates greater than 100 beat/min the stroke volume fell by more than 15%. This drop in stroke volume began at approximately 50% of the maximum external work completed. The stroke volume at maximum exercise in Group B was significantly less than that in Group A patients (Fig 18).

The remaining twelve patients (Group C) failed to increase the stroke volumes significantly during exercise (i.e. stroke volume increased by less than 30% above resting value). One patient in this group exhibited a decrease in stroke volume with the commencement of exercise. Further analysis of the data from the thirty-nine patients was based upon this initial classification based upon stroke volume responses.

Comparison of the Exercise Response Between Groups A, B and C (Fig 19,20,21,22).

Patients in Group A showed increases in heart rate, stroke volume and cardiac output in a manner similar to the normal controls. The changes in the mean arterial pressure were also similar, while the calculated systemic vascular resistance was higher at rest in the patient subsets than in the normal controls (Fig 21,22). The patients in Group B showed comparable changes in heart rate, stroke volume and cardiac output until a load of 70W was completed. At higher workloads the cardiac outputs and stroke volumes tended to be lower while the heart rates were higher in Group B than in Group A patients (Fig 18,19,20). The mean arterial pressure in Group B patients was significantly higher than in Group A both at rest and during exercise (Fig 21). Thus, in Group B, the peripheral vascular resistance was increased both at rest and during exercise when compared to Group A patients (Fig 22).

The patients in Group C had a significantly higher mean heart rate throughout exercise than the Group A patients (Fig 19). However, since the mean stroke volume in these patients was unchanged compared with the resting values the cardiac output remained consistently lower than was the case in the other groups studied for all levels of exercise. The mean arterial pressure in the Group C patients was similar to that of the patients in Group A while at rest but was consistently higher during exercise. The calculated peripheral resistance was increased only during exercise. These findings are summarized in Figure 19,20,21 and 22.

Correlation of the stroke volume classification with clinical data

The clinical data in these 39 patients revealed no differences in age, ejection fraction measured at rest or the peak plasma creatine kinase at the time of infarction between the Groups (Table III). Patients in Group C completed a lower workload than patients in the other two groups, however, the conventional end-points for the exercise tests were not significantly different in the three Groups (Table III). More patients in Group B and C had a previous history of myocardial infarction or angina than did Group A patients (Table IV).

Echocardiographic studies completed on the same day as the exercise test indicated that 25 patients of the total study group (n=39) had evidence of an inferior wall infarction. Eight of these 25 patients exhibited asynergy of the left ventricular inferior wall only and of the 8 patients, 4 exhibited normal stroke volume responses during exercise (Group A). The remaining 17 patients with inferior wall infarction had evidence of right ventricular involvement. Fourteen of these patients exhibited abnormal stroke volume responses to exercise and were consequently classified into Group B (n=7) or Group C (n=7) (Table IV).

A retrospective analysis was completed in 26 of the 39 patients in the study group who had undergone ventricular angiography and coronary arteriography within the first year following the acute event. The score for the severity of the coronary lesions was lower in Group A than in the other 2 patient subsets with the score for Group C being significantly higher than that for Group A. Left ventricular end-diastolic and end-systolic volume indices were also greater in

Groups B and C than in Group A with the end-diastolic volume index difference between Group A and C reaching significance (Table IV).

Discussion

This study was undertaken to examine the changes in stroke volume observed during upright exercise in patients recovering from myocardial infarction. All the patients examined had recovered from a myocardial infarction 8-10 weeks previously and had undergone a low level exercise test before discharge from hospital, approximately 10 days after the acute episode. Patients who exhibited overt cardiac failure, significant arrhythmias, persistent hypotension or unstable angina at the time of discharge from the hospital were excluded from the study (Fig 17) (11). These exclusions ensured that the patients studied were those in the New York Heart Association Classes I and II and hence had a relatively good prognosis (12).

Within this homogenous group of relatively low risk patients there was a significant number of patients who deviated from the normal response in terms of the changes in stroke volume during upright exercise. Approximately 38% of the patients yielded curves similar to those of normal individuals. The responses in the remaining 62% were abnormal.

In patients recovering from myocardial infarctions, abnormalities in the stroke volume responses induced by upright exercise may result from a number factors. These include i) the extent and location of the damaged myocardium, ii) the severity of the underlying coronary artery disease, iii) the residual function of the myocardium and iv) neurohumoral adjustments to exercise. In addition, the severity of the exercise undertaken and the overall degree of physical conditioning may also play a part.

Left ventricular infarctions were distributed equally between these three groups (Table III and IV). However, the possible influence of the right ventricle on left ventricular function is of interest in the present investigation. It has been demonstrated in man that right ventricular infarction occurring in conjunction with an acute inferior wall infarction may result in a low cardiac output associated with elevated right ventricular filling pressures (13). Subsequent studies in animals with similar infarcts have suggested that the pericardium together with a leftward septal shift may limit left ventricular filling due to a reversal of the transseptal pressure gradient (14). In the present investigation, 17 of the 25 patients with inferior wall infarction had evidence of right ventricular involvement on echocardiography and 14 of these patients exhibited an abnormal stroke volume response and were classified into Group B or C. Only 3 of the 17 patients exhibited a normal stroke volume profile during exercise and were therefore placed in Group A (Table IV).

When considering the severity of the underlying coronary artery disease and the residual function of the myocardium, it becomes apparent that there is trend toward more extensive lesions and more severe left ventricular dysfunction in Groups B and C compared with Group A, the comparison between Group A and Group C reaching significance (Table IV).

Residual left ventricular function following myocardial infarction can be evaluated by assessing the determinants of stroke volume. As the venous return increases during upright exercise in normal subjects the concurrent increase in stroke volume could be viewed as a utilization of the stroke volume reserve, resulting from a combination of the Starling mechanism, an increase in the contractile state and a reduction in peripheral vascular resistance (15). In patients, an abnormal stroke volume response could occur due to exhaustion of these mechanisms. For example, when the Starling mechanism is exhausted and the inotropic response is limited, stroke volume becomes very sensitive to afterload (16). It appears that Group C patients who are likely to have more severe ventricular dysfunction are at the limit of their stroke volume reserve while at rest, and therefore are unable to increase it with exercise. In Group B patients, the point at which the stroke volume reserve is exhausted is at a load which requires a heart rate of greater than 100-105 beat/min.

Possible Role of the Neurohumoral Responses to Exercise

The studies of Kaufman et al (17,18,19) have indicated that the afferent information conveyed by Group III and Group IV muscle afferent nerve fibers respond to metabolites accumulating in exercising muscle. It is thought that this afferent information influences the central command in the neural regulation of the circulation during exercise (20). The consequence of this input would be to increase the sympathetic drive to the heart and the blood vessels. The former would serve to increase the rate of the heart while the latter would tend to produce vasoconstriction and hence an increase in vascular resistance in the non-exercising regions.

At the submaximal levels of exercise examined in this study, the cardiac output is maintained at an appropriate level in normal subjects and Group A patients by increasing both heart rate and stroke volume. However, the Group C patients exhibit poor ventricular function and are unable to increase stroke volume during exercise. When the cardiac output fails to rise appropriately, the afferent information from the exercising muscle tends to increase the heart rate and enhance the sympathetic drive to the periphery resulting in an increase in arterial pressure during exercise and a relative increase in peripheral resistance. The enhanced sympathetic drive to the non-exercising tissues would tend to shunt a greater proportion of the cardiac output into the exercising muscles (21).

The situation in the patients in Group B could be examined in a similar fashion. The left ventricle is capable initially of increasing the stroke volume but at workloads greater than 70W, the stroke volume decreases. This observation could well be due to the onset of silent ischemia (22,23). Also, in patients with inferior infarction involving the right ventricle, the septum may encroach upon the lumen of the left ventricle compromising its filling at these levels of exercise (24). Regardless of the mechanism, when the stroke volume reserve is exceeded the cardiac output falls. At this stage, patients could increase the heart rate by reflexes mediated by Group III and IV afferent fibers. In fact, the heart rate appeared to increase at loads of 90W and greater in the patients in Group B.

Group B patients exhibit a significantly higher vascular resistance both at rest and during graded exercise than the normal subjects and Group A patients (Fig 22). The enhanced vascular resistance may be explained by the same mechanism postulated in Group C during exercise. However, it is possible that the higher vascular resistance at rest and during exercise in these patients may be mediated by neurohumoral mechanisms (25). Cardiopulmonary receptors with unmyelinated vagal afferent fibers appear to exert a tonic inhibitory influence on peripheral sympathetic nerve activity, therefore, on the arterial pressure and vascular resistance. Removal of this influence by infarction may result in an increased sympathetic outflow which can lead to changes in the arterial pressure and the release of renin and vasopressin (25,26).

The results of the present study indicate that all patients in a particular functional class do not make the same adjustments to graded upright exercise. Further, the construction of the stroke volume-heart rate profiles could be of value in planning further management and as a prognostic indicator for asymptomatic post infarction patients. In addition, it is suggested that ventricular function should be taken into consideration when planning training regimes (27) and when afterload reducing therapies are contemplated. Further study is required to delineate the neural and humoral adjustments which may be present within and between these groups who exhibit abnormal ventricular function during exercise.

TABLE III

CLINICAL DATA

	GROUP A	GROUP B	GROUP C
	N = 14	N = 13	N = 12
AGE	55.6±2.6	53.9±2.4	52.9±3.7
RESTING EF[1]	43.5±3.7	42.3±3.1	43.5±3.5
LOCATION MI (ECG)[2]			
ANTERIOR	N=6(43%)	N=4(31%)	N=3(25%)
INFERIOR	N=8(57%)	N=9(69%)	N=8(67%)
SUBEND[3]	-	-	N=1 (8%)
PEAK CK[4]	1042.0±348	1669.1±245	1612.9±278
NORRIS INDEX[5]	3.4±.3	3.8±.7	2.7±.5
EXERCISE DATA			
MAX WORKLOAD	99.3±8.0	102.3±5.8	85.0±5.0
ABNORMAL B.P.	N=0	N=3(23%)	N=3(25%)
ISCHAEMIA[6]	N=3(21.4%)	N=3(23.1%)	N=6(50%)

[1] Ejection Fraction Measured By Radionuclide Ventriculography (8,9)

[2] Electrocardiography

[3] Subendocardial Infarction

[4] Peak Creatine Kinase (iu/l)

[5] Norris Index (Ref. 28)

[6] ECG ST segment depression of > 1mm

TABLE IV

CLINICAL DATA

	GROUP A	GROUP B	GROUP C
	n=14	n=13	n=12
History of MI	1	4	1
History of Angina > 3 months	1	6	4
History of Hypertension	1	3	3
History of Smoking	9	13	11
Location MI (Echo)			
Ant.	6	3	3
Ant. & Inf.		1	1
Inferior Wall Without RV*	4	3	1
Inferior Wall with RV*	3	7	7
No asynergy	1		**1
DATA FROM ANGIOGRAPHY			
		$p<0.05$	
***Score for Coronary Lesions	46.2±11.3	63.1±12.9	72.4±10.7
		$p<0.05$	
End-Diastolic Volume Index (ml/m^2)	89.5±7.4	96.7±13.6	111.1±5.8
End-Systolic Volume Index (ml/m^2)	40.9±6.6	45.1±11.7	57.6±9.0

* RV=Right ventricle involvement

** Patient exhibited evidence of LVH

*** Ad Hoc committee of the American Heart Association 1973 (6)

Figure 17

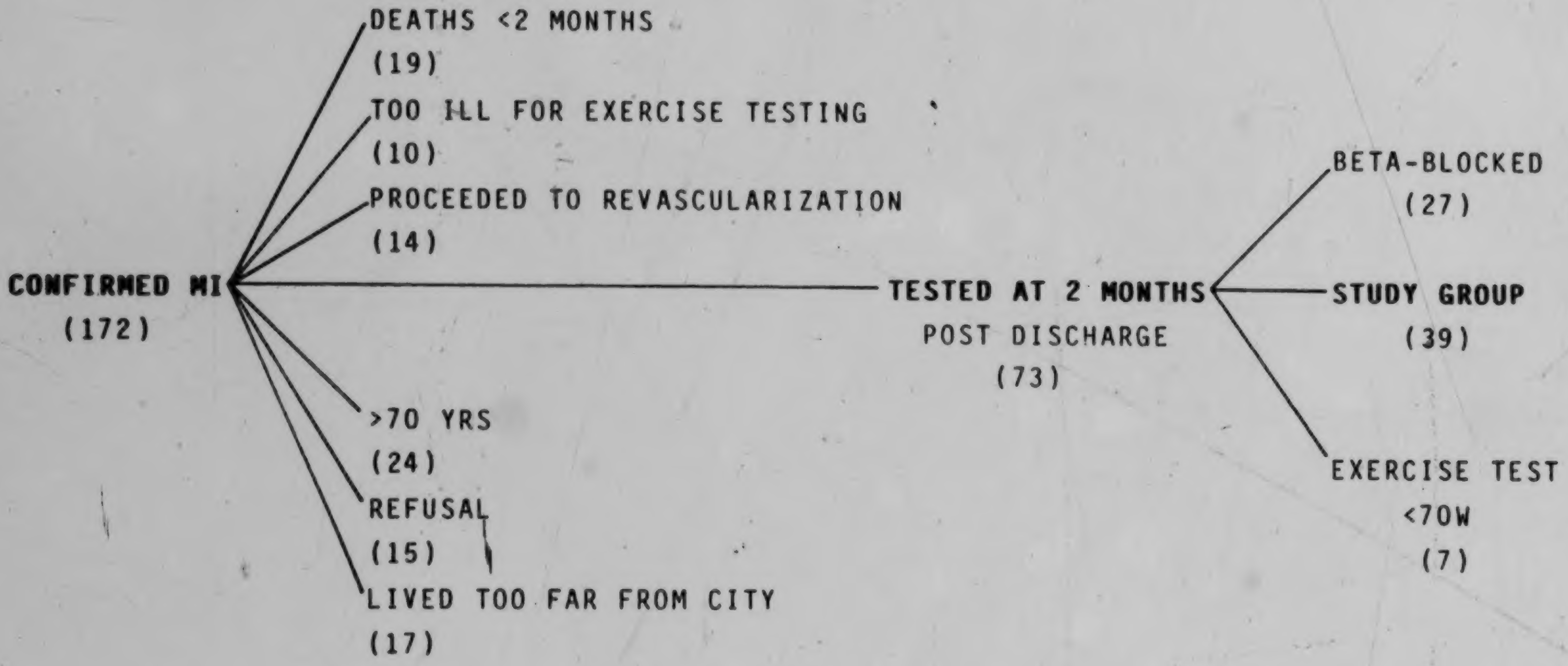
REASONS FOR PATIENT EXCLUSION FROM THE INVESTIGATION:

Distribution of patients in study.

The numbers of patients in each category are given in parenthesis.

REASONS FOR PATIENT EXCLUSION FROM PRESENT INVESTIGATION

POPULATION STUDIED



CONFIRMED MI
(172)

DEATHS <2 MONTHS
(19)

TOO ILL FOR EXERCISE TESTING
(10)

PROCEEDED TO REVASCULARIZATION
(14)

>70 YRS
(24)

REFUSAL
(15)

LIVED TOO FAR FROM CITY
(17)

TESTED AT 2 MONTHS
POST DISCHARGE
(73)

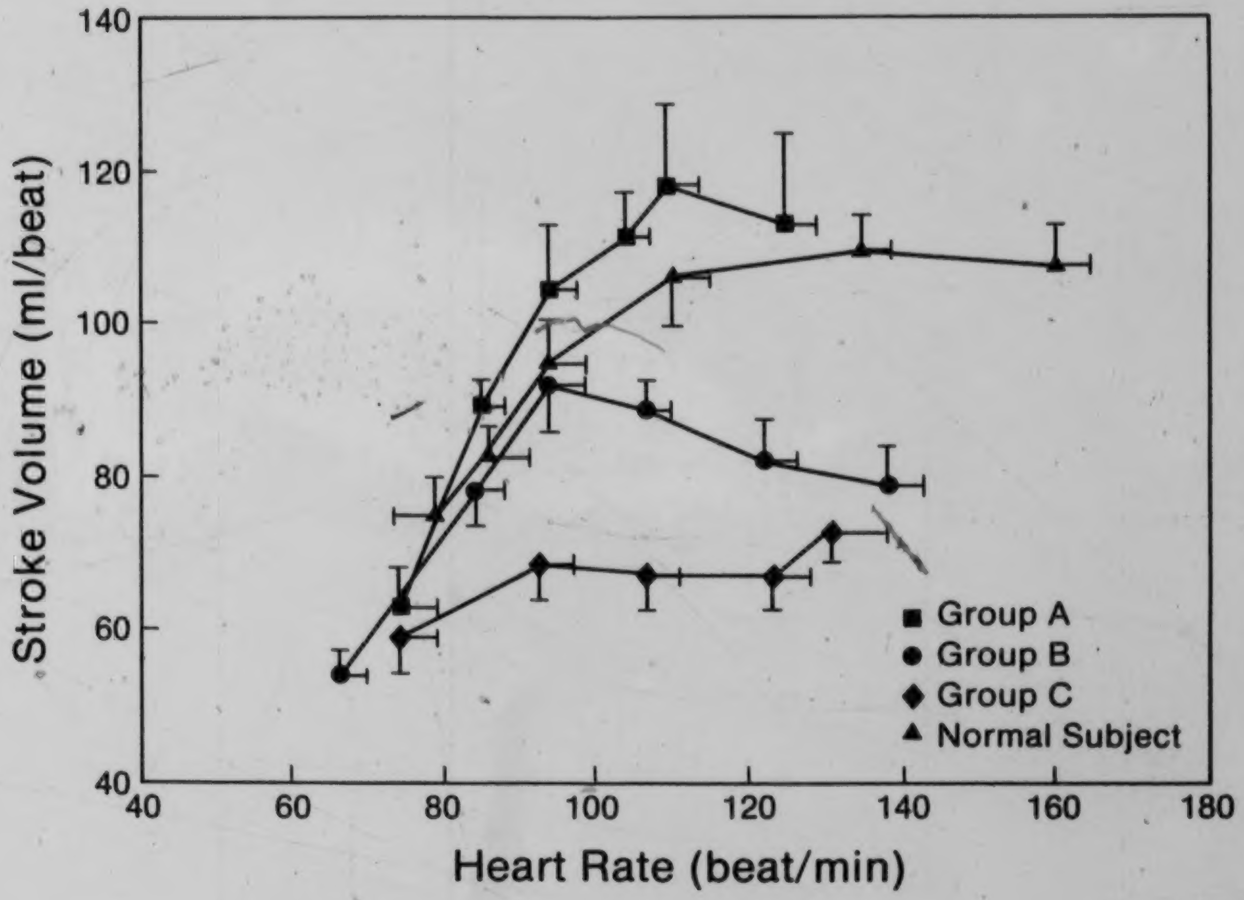
BETA-BLOCKED
(27)

STUDY GROUP
(39)

EXERCISE TEST
<70W
(7)

Figure 18

STROKE VOLUME-HEART RATE RESPONSE IN POST INFARCTION PATIENTS AND THE CONTROL GROUP: Changes in stroke volume and heart rate in post myocardial infarction patients and normal sedentary subjects during graded upright exercise on a bicycle ergometer. Ordinate: stroke volume (ml/beat), abscissa: heart rate (beat/min). The post infarction patients exhibited three patterns of changes in stroke volume (Normal subjects: n=9; Group A: n=14; Group B: n=13; Group C: n=12). The values shown are mean ± SEM and each point is derived from the coordinates for the workloads defined in the protocol.



Stroke Volume (ml/beat)
140
120
100
80
60
40
40
60
80
100
120
140
160
180
Heart Rate (beat/min)
■ Group A
● Group B
◆ Group C
▲ Normal Subject

Figure 19

HEART RATE DURING EXERCISE IN POST INFARCTION PATIENTS AND THE CONTROL GROUP: The heart rate response during upright graded exercise on the bicycle ergometer in normal sedentary subjects and post infarction patients who were classified into Groups A, B and C. Ordinate: heart rate (beat/min); abscissa: workload (watt). Values shown are mean ± SEM. At 70W the heart rate was significantly higher in Group C (†) than in A and B ($p<0.01$). At 90W the heart rate in both Groups B and C (*) were greater than that in A ($p<0.05$).

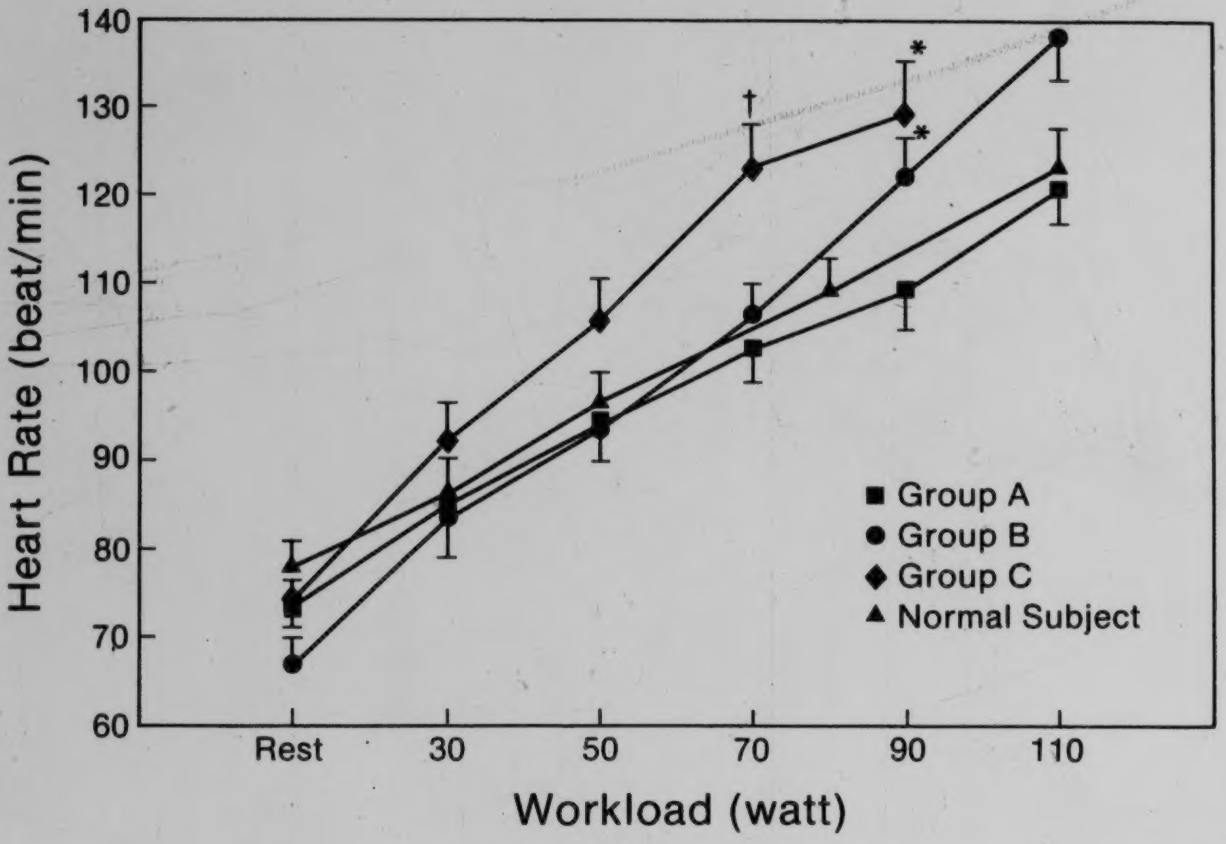

Heart Rate (beat/min)
140
130
120
110
100
90
80
70
60
Rest
30
50
70
90
110
Workload (watt)
†
*
*
■ Group A
● Group B
◆ Group C
▲ Normal Subject

Figure 20

CARDIAC OUTPUT RESPONSE DURING EXERCISE IN POST INFARCTION PATIENTS AND THE CONTROL GROUP: The cardiac output response during upright graded exercise on the bicycle ergometer in normal sedentary subjects and post infarction patients who were classified into Groups A, B and C. Ordinate: cardiac output (1/min); abscissa: workload (watt). Values shown are mean ± SEM. At 50W (*) the 70W (†) the cardiac outputs were significantly lower in Group C than in A and B ($p<0.05$ and <0.01 respectively). At 90W the cardiac outputs in both Groups B and C (*) were significantly lower than that in A ($p<0.05$).

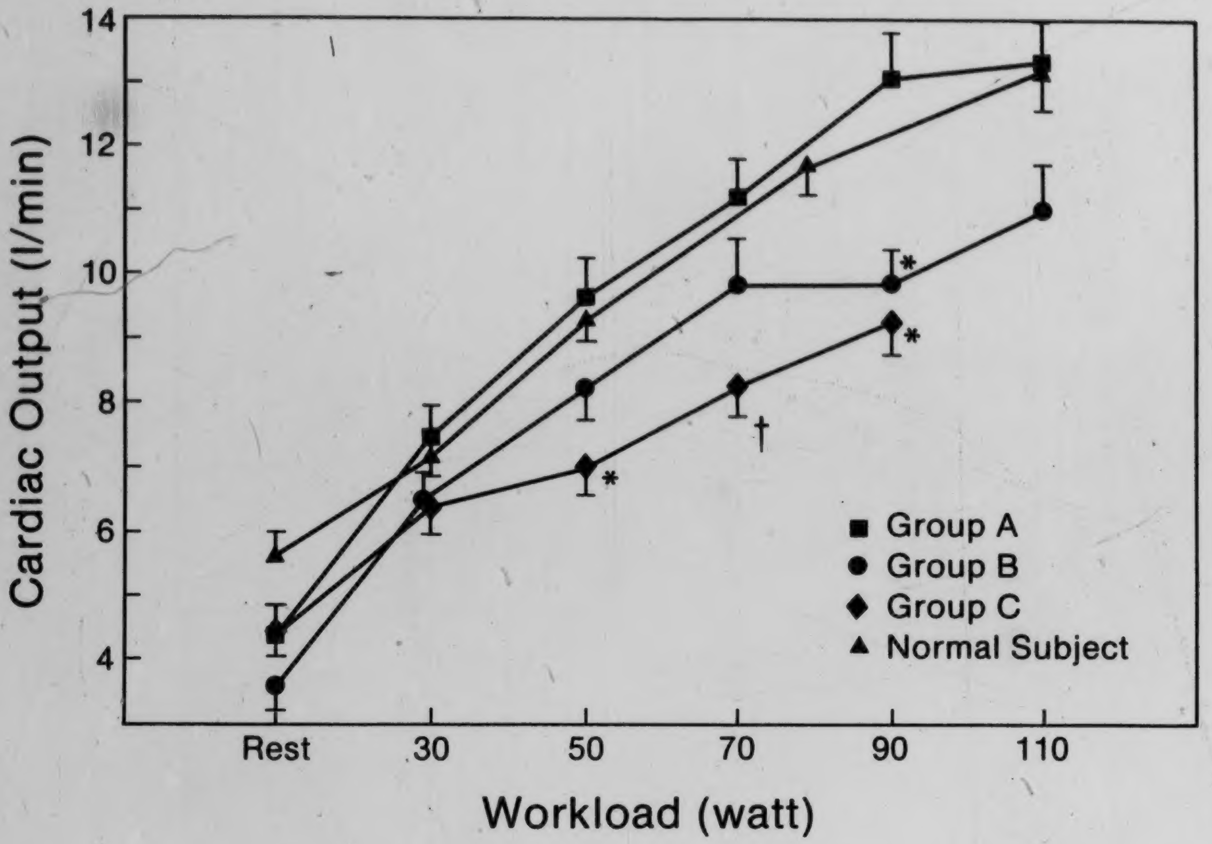

Cardiac Output (l/min)
14
12
10
8
6
4
Rest
30
50
70
90
110
Workload (watt)
■ Group A
● Group B
◆ Group C
▲ Normal Subject
*
*
*
†

Figure 21

MEAN ARTERIAL PRESSURE DURING EXERCISE IN POST INFARCTION PATIENTS AND THE CONTROL GROUP: The mean arterial pressure response during upright graded exercise on the bicycle ergometer in normal sedentary subjects and post infarction patients who were classified into Groups A, B and C. Ordinate: mean arterial pressure (mm Hg); abscissa: workload (watt). Values shown are mean ± SEM. At 50W (*), 70W (*) and 90W(*) the mean arterial pressures were significantly greater in Group B than in A $(p<0.05)$.

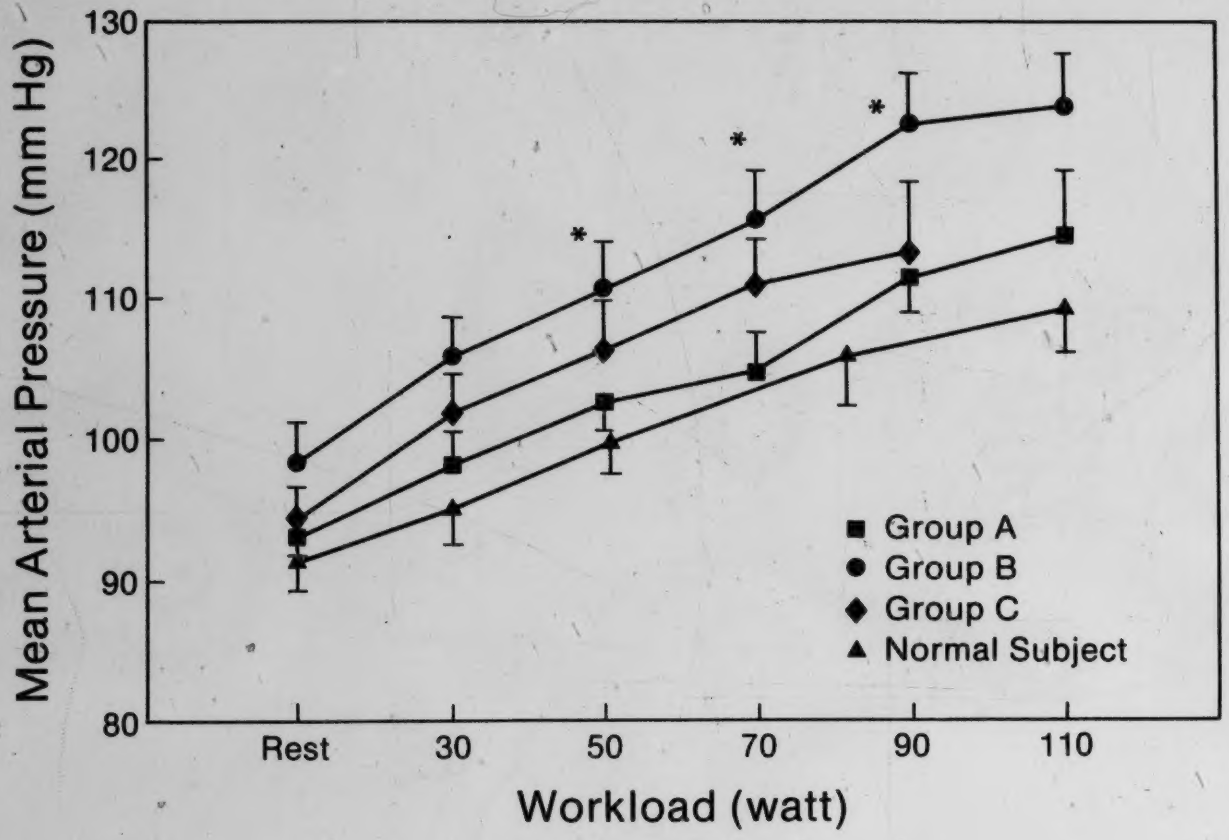
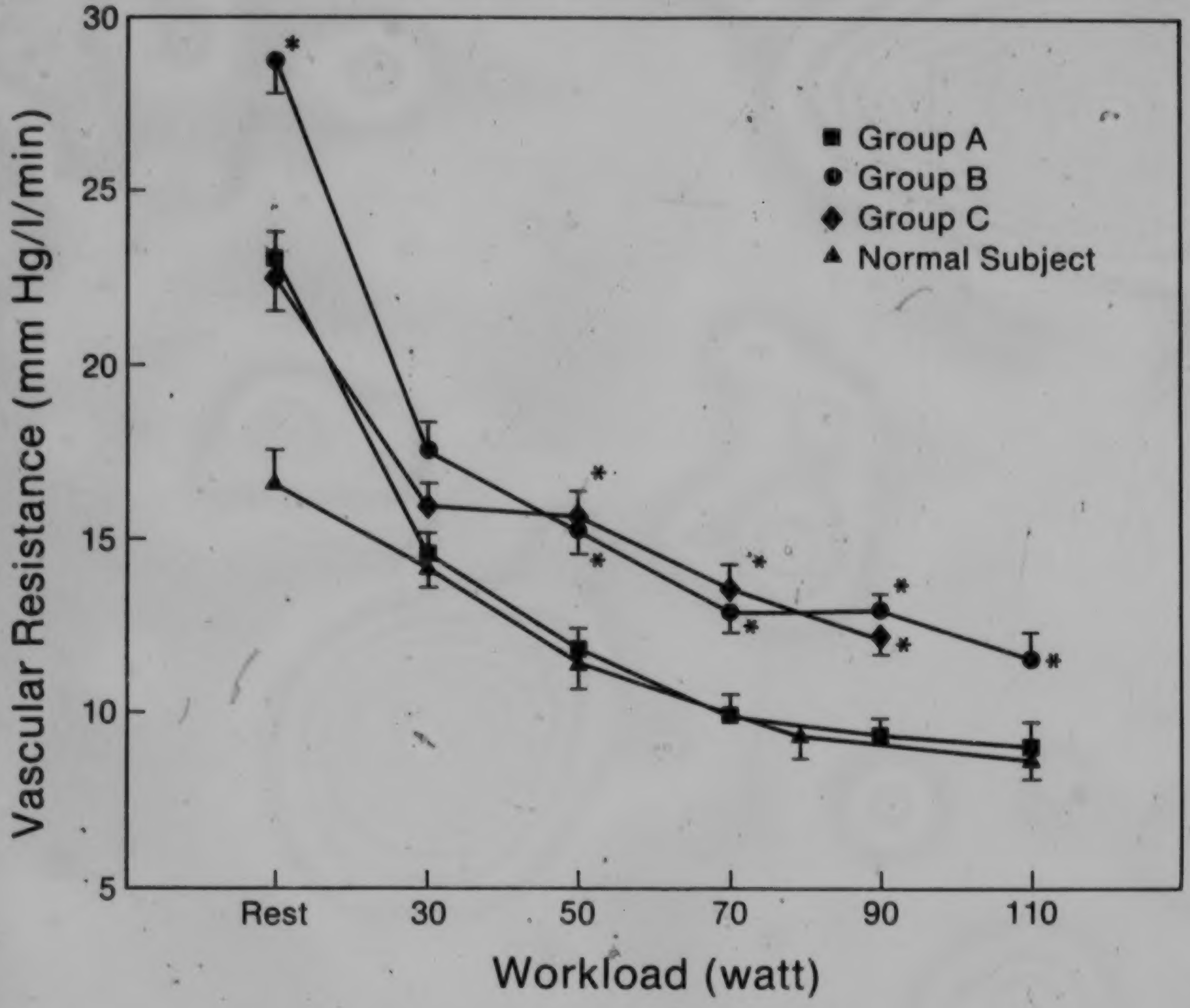

Mean Arterial Pressure (mm Hg)
130
120
110
100
90
80
Rest
30
50
70
90
110
Workload (watt)
*
*
*
■ Group A
● Group B
◆ Group C
▲ Normal Subject

Figure 22

SYSTEMIC VASCULAR RESISTANCE DURING EXERCISE IN POST INFARCTION PATIENTS AND THE CONTROL GROUP: The systemic vascular resistance response during upright graded exercise on the bicycle ergometer in normal sedentary subjects and post infarction patients who were classified into Groups A, B and C. Ordinate: vascular resistance (mm Hg/l/min); abscissa: workload (watt). Values shown are mean ± SEM. At rest all three groups had a higher vascular resistance than the normal subjects and tahe values in B (*) were greater than that in A and C ($p<0.05$). At 50W, 70W and 90W the values in Groups B (*) and c (*) were significantly higher than those in Group A and the normal subjects. At 110 W Group B was significantly higher that the value in Group A and the normal subjects.


30
25
20
15
10
5
Vascular Resistance (mm Hg/l/min)
Rest
30
50
70
90
110
Workload (watt)
■ Group A
● Group B
◆ Group C
▲ Normal Subject
*

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CHAPTER VI

GENERAL DISCUSSION AND CONCLUSIONS

The results from this series of investigations indicates that impedance cardiography provides a simple and reliable means of obtaining repeated hemodynamic data during maximal and submaximal upright exercise in both normal subjects and in patients with known coronary artery disease. In addition, changes in stroke volume can be easily and quickly determined throughout the exercise period with little discomfort to the patient. In the present series of studies, sequential measurements were obtained during a single exercise test which permitted the construction of curves relating stroke volume to heart rate. This information may be useful in determining prognosis for individual patients and for prescribing appropriate long term therapy in patients with coronary artery disease.

The conventional methods of assessing ventricular function non-invasively are radionclide scintigraphy (1,2) and echocardiography (3). Gated radionuclide ventriculography could be used to generate sequential data during exercise similar to that obtained using impedance cardiography, however, it is cumbersome and expensive. While radionuclide studies are usually performed in the semi-recumbent position, echocardiography can be done in the upright posture. Echocardiography is a technique that requires a considerable degree of technical expertise and expensive equipment. Both these techniques exhibit a random error for stroke volume during rest and exercise that is comparable to that of impedance cardiography (3). However, there are no reported studies in which either of these techniques were compared to a standard technique such as the direct Fick method during graded upright exercise. Impedance cardiography is a simple method compared to other non-invasive techniques for assessing stroke volume during exercise. In addition it is less expensive and is as reliable as these other methods.

This series of studies also indicates that all asymptomatic patients who have suffered a previous myocardial infarction do not respond to upright graded exercise in an identical manner. About 60-70% of this patient population exhibit an abnormal stroke volume response which is manifested only during exercise. Whether identification of left ventricular dysfunction during exercise as defined in this study is of clinical importance is yet unknown.

Thus, future research questions needed to investigate the clinical application of the present findings are:

1. Is the stroke volume-heart rate relationship determined during graded exercise of prognostic value?
2. Are the stroke volume-heart rate curves useful in planning therapy in patients who have suffered a previous infarction?
3. Can these stroke volume-heart rate curves be used to monitor drug therapy?
4. Do changes in the stroke volume during exercise as measured by impedance cardiography compare favorably with other clinically accepted methods of determining ventricular volumes?

5. What are the humoral and neural mechanisms underlying the 3 patient subsets delineated in the studies described here?

6. Does the ventricular function as determined by impedance cardiography predict the coronary anatomy?

7. In a prospective study of patients with an infarction of the left inferior wall in addition to right ventricular involvement, do patients exhibit an abnormal stroke volume response during graded upright exercise?

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CURRICULUM VITAE

NAME: Dorothy Maxine Hetherington

ADDRESS: 12304 - 28 Avenue
Edmonton, Alberta
T5J 4E4

BIRTHDATE: February 2, 1945

CITIZENSHIP: Canadian

MARITAL STATUS: Married (three children)

ACADEMIC RECORD:

Present	Graduate Studies in Medical Science, University of Alberta, Division of Cardiology Medicine
1980	B.Sc. (Honors) in Physiology, University of Alberta
1976 - 1978	Graduate Studies in Exercise Physiology, University of Ottawa (studies incomplete due to a move to Edmonton)
1970	B.Sc.N., University of Alberta
1966	R.N., University of Alberta Hospitals

PUBLICATIONS:

1. Teo, K.K., Hetherington, M., Haennel, R., Greenwood, P., Rossall, R.E., & Kappagoda, C.T. Cardiac output measured by impedance cardiography during maximal exercise tests. Cardiovascular Research, 1985; 19:737-743.

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CONTINUING EDUCATION:

August 1981	Dr. Marriott's Advanced Electrocardiography, Victoria, British Columbia
June 1981	E.C.G. Workshop, MacDonald Hotel, Edmonton, Alberta
July 1980	Dr. Marriott's Introductory Electrocardiography, Edmonton, Alberta
1975	International Symposium on Cardiac Rehabilitation, Toronto, Ontario
1974	Symposium of Adult Fitness and Cardiac Rehabilitation, LaCrosse, Wisconsin

WORKSHOPS PRESENTED:

September - October 1985	Understanding Electrocardiogrpahy. Presented for Nursing Health Science Inc. in Edmonton, Calgary, Red Deer, Vancouver, Victoria, Grande Prairie and Lloydminster (94 hours)
February 1985	Cardiology Workshop. Presented for Health and Welfare Canada, Inuvik, North West Territories (12 hours)
May - June 1984	Understanding Electrocardiography I. Presented for Grant MacEwan Community College, Alberta Association of Certified Technologists, and Nursing Health Science Inc., Edmonton, Calgary, Red Deer and Lethbridge (48 hours)
May 1984	Advanced Clinical Cardiovascular Physiology for Nurses. Presented for Nursing Health Science Inc., Vancouver, Victoria, Saskatoon, Regina and Calgary (30 hours)

May 1984	Cardiology Workshop. Presented for Faculty of Extension, University of Alberta in St. Paul, Alberta (6 hours)
February 1984	Advanced Clinical Cardiovascular Physiology presented for Nursing Health Science Inc., Edmonton, Red Deer and Calgary (36 hours)
Spring 1984 Fall 1983 Spring 1983	Advanced Clinical Cardiopulmonary Physiology, Instructor, Faculty of Extension, University of Alberta (12 hours)
March 1983 - April 1983	Critical Care Nursing Series Instructor, Grant MacEwan Community College (20 hours)

NURSING EXPERIENCE:

1982 - 1983	*Post Graduate Critical Care Nursing Program Instructor, University of Alberta Hospitals (full time)
1980 - 1982	*Post Graduate Cardiovascular Intensive Care Nursing Program Instructor, University of Alberta Hospitals (full time)
	*June, 1982 - the name of the Post Graduate Cardiovascular Intensive Care Nursing Program was changed to Post Graduate Critical Care Nursing Program
1979 - 1980	Nursing Float Pool, University of Alberta Hospitals, Edmonton
Fall 1976	Cardiac Rehabilitation Program Volunteer, University of Ottawa
1975 - 1976	Cardiovascular Surgery Instructor (part time), Faculty of Nursing, Laurentian University
19175 - 1976	Volunteer Committee Member to organize a Cardiac Rehabilitation Program, Sudbury, Ontario
January - June 1975	Children's Treatment Centere, Sudbury, Ontario (full time)
May - December 1974	Research Assistant - Exercise Physiology, Laurentian University (part time)

1970	Edmonton Cardiac Fitness Institute (part time)
Summer 1970	Cardiology (Station 41), University of Alberta Hospitals (full time)
Summer 1969	General Surgery (Station 51), University of Alberta Hospitals (full time)
Summer 1968	Neurosurgery, University of Alberta Hospitals (full time)
January - April, 1968	General Surgery, Jeffery Hales Hospital, Quebec City (full time)
May - December 1967	Urology, University of Alberta Hospitals (full time)
October 1966 - March 1967	Intensive Care Unit, Calgary General Hospital (full time)